PB87-117420

Health Assessment Document for Hydrogen Sulfide, Review Draft

(U.S.) Environmental Protection Agency
Washington, DC

Aug 86

U.S. Department of Commerce
National Technical Information Service
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TECHNICAL REPORT DATA
(Please read Instructions on the reverse before completing)

1. REPORT NO. EPA/600/8-86/026A	2.
3. RECIPIENT'S ACCESSION NO. PB87 117420/AS	
4. TITLE AND SUBTITLE Health Assessment Document for Hydrogen Sulfide	5. REPORT DATE August 1986
	6. PERFORMING ORGANIZATION CODE EPA/600/23
7. AUTHOR(S) See list of authors, contributors, and reviewers.	8. PERFORMING ORGANIZATION REPORT NO.
9. PERFORMING ORGANIZATION NAME AND ADDRESS Environmental Criteria and Assessment Office (MD-52) Office of Health and Environmental Assessment (ORD) U.S. Environmental Protection Agency Research Triangle Park, N.C. 27711	10. PROGRAM ELEMENT NO.
	11. CONTRACT/GRANT NO.
12. SPONSORING AGENCY NAME AND ADDRESS Office of Health and Environmental Assessment Office of Research and Development U.S. Environmental Protection Agency Washington, D.C. 20460	13. TYPE OF REPORT AND PERIOD COVERED Health Assessment
	14. SPONSORING AGENCY CODE EPA/600/21
15. SUPPLEMENTARY NOTES	

16. ABSTRACT Hydrogen sulfide is a highly toxic gas which is immediately lethal in concentrations greater than 2000 ppm. This toxic end-point is due to anoxia to brain and heart tissues which results from its interaction with the celluar enzyme cytochrome oxidase. Inhibition of this enzyme halts oxidative metabolism which is the primary energy source for cells. A second toxic end-point is the irritative effect of hydrogen sulfide on mucous membranes, particularly edema at sub-lethal doses (250 to 500 ppm) in which sufficient exposure occurs before conciousness is lost. Pulmonary edema has been reported at long-term exposure to levels as low as 50 ppm. Irritation to the eye at concentrations above 50 ppm, can cause initial loss of coronary reflex, changes in visual acuity and perception of blue or rainbow colors around lights, followed by very painful manifestation of inflammation, with ulceration in severe cases. Olfactory sensation is lost at 150-200 ppm, so that the characteristic odor of rotten eggs is insufficient warning of lethal exposure. Recovered victims of exposure report neurologic symptoms such as headache, fatigue, irritability, vertigo, and loss of libido. Long-term effects are similar to those caused by anoxia due to other toxic agents like CO, and probably are not due to specific H_2S effects. H_2S is not a cumulative poison. No mutagenic, carcinogenic, reproductive or teratogenic effects have been reported in the literature.

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group

18. DISTRIBUTION STATEMENT Release to Public	19. SECURITY CLASS (This Report) Unclassified	21. NO. OF PAGES 96
	20. SECURITY CLASS (This page) Unclassified	22. PRICE

EPA Form 2220-1 (Rev. 4-77) PREVIOUS EDITION IS OBSOLETE

United States Environmental Protection Agency

Office of Health and Environmental Assessment Washington DC 20460

EPA/600/8-86/026A
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Research and Development

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EPA

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SPRINGFIELD, VA. 22161

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U.S. ENVIRONMENTAL PROTECTION AGENCY
Office of Health and Environmental Assessment
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Research Triangle Park, NC 27711

DISCLAIMER

This document is an external draft for review purposes only and does not constitute Agency policy. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

PREFACE

The Office of Health and Environmental Assessment has prepared this health assessment to serve as a source document for EPA use. The health assessment was originally developed for use by the Office of Air Quality Planning and Standards to support decision making regarding possible regulation of hydrogen sulfide as a hazardous air pollutant. However, the scope of this document has since been expanded to address multimedia aspects.

In the development of the assessment document, the scientific literature has been inventoried, key studies have been evaluated, and summary/conclusions have been prepared so that the chemical's toxicity and related characteristics are qualitatively identified. Observed effect levels and other measures of dose-response relationships are discussed, where appropriate, so that the nature of the adverse health responses is placed in perspective with observed environmental levels.

The relevant literature for this document has been reviewed through July, 1986.

Any information regarding sources, emissions, ambient air concentrations, and public exposure has been included only to give the reader a preliminary indication of the potential presence of this substance in the ambient air. While the available information is presented as accurately as possible, it is acknowledged to be limited and dependent in many instances on assumption rather than specific data. This information is not intended, nor should it be used, to support any conclusions regarding risk to public health.

If a review of the health information indicates that the Agency should consider regulatory action for this substance, a considerable effort will be undertaken to obtain appropriate information regarding sources, emissions, and ambient air concentrations. Such data will provide additional information for drawing regulatory conclusions regarding the extent and significance of public exposure to this substance.

ABSTRACT

Hydrogen sulfide is a highly toxic gas which is immediately lethal in concentrations greater than 2000 ppm. This toxic endpoint is due to anoxia in brain and heart tissues which results from its interaction with the cellular enzyme cytochrome oxidase. Inhibition of this enzyme halts oxidative metabolism which is the primary energy source for cells. A second toxic endpoint is the irritative effect of hydrogen sulfide on mucous membranes, particularly those of the respiratory tract and the eyes. Respiratory irritation causes pulmonary edema at sublethal doses (250 to 500 ppm) in which sufficient exposure occurs before consciousness is lost. Pulmonary edema has been reported at long-term exposure to levels as low as 50 ppm. Irritation to the eye at concentrations above 50 ppm, can cause initial loss of coronary reflex, changes in visual acuity and perception of blue or rainbow colors around lights, followed by very painful manifestation of inflammation, with ulceration in severe cases. Olfactory sensation is lost at 150-200 ppm, so that the characteristic odor of rotten eggs is insufficient warning of lethal exposure. Recovered victims of exposure report neurologic symptoms such as headache, fatigue, irritability, vertigo, and loss of libido. Long-term effects are similar to those caused by anoxia due to other toxic agents like CO, and probably are not due to specific H_2S effects. Hydrogen sulfide is not a cumulative poison. No mutagenic, carcinogenic, reproductive or teratogenic effects have been reported in the literature.

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Technical assistance was also provided by Northrop Services: Mr. John Bennett, Ms. Kathryn Flynn, Ms. Miriam Gattis, Ms. Lorrie Godley, Ms. Patricia Tierney, Ms. Varetta Powell, and Ms. Jane Winn-Thompson.

Technical assistance was also provided by Deborah Staves of Systems Research and Development Corporation (SRD), with the assistance of Sharon Stubbs and Mary Williams.

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1. SUMMARY AND CONCLUSIONS

1.1 BACKGROUND INFORMATION

Hydrogen sulfide (H_2S) is a colorless gas with a characteristic obnoxious odor like that of rotten eggs, at low concentration. Its molecular weight is 34.08, and with a specific gravity of 1.192 it is heavier than air. It is flammable in air, can explode, and can be ignited by static discharge. It burns with a pale blue flame, and its combustion products are sulfur dioxide and water. Hydrogen sulfide is the only thermodynamically stable binary sulfur-hydrogen compound that occurs frequently in nature, and because of its relative lack of hydrogen bonding it is a gas under normal conditions. It is soluble in water and in a number of organic compounds.

Produced in nature primarily through the decomposition of organic material by bacteria, hydrogen sulfide is also a constituent of natural gas, petroleum, sulfur deposits, volcanic gases and sulfur springs. Such natural sources constitute approximately 90 percent of the air burden of hydrogen sulfide, which has been estimated to be 90 to 100 million tons annually.

Industrial sources and other anthropogenic activities contribute about 10 percent to the total air burden of hydrogen sulfide. In the United States, 125,000 employees in 73 industries are potentially exposed to H_2S, according to the National Institute of Occupational Safety and Health. The gas is used mainly as an intermediate and reagent in the preparation of other compounds of reduced sulfur. It is also a by-product of many industrial processes that release it into the atmosphere. It generally is not found in high concentrations in the ambient air. Occasional catastrophic releases in processing and transport have exposed the general public to concentrations high enough to elicit toxic symptoms and death.

Hydrogen sulfide reacts with photochemically generated free radicals, especially ·OH, and is oxidized by them. It has a lifetime in air ranging from 12 to 37 hours, but this varies depending on presence of photoactive pollutants and temperature, so that seasonal and geographic differences in concentrations are found.

Ambient levels of H_2S tend to be low, in the range of 0.001 mg/m^3 (0.0014 ppm). Pollution episodes have reached levels of nearly 0.5 mg/m^3 (0.7 ppm) in severe cases, and accidental releases such as well blowouts have produced levels as high as 14.3 mg/m^3 (20 ppm). At least one release in Poza Rica, Mexico emitted lethal levels of gas.

Ecologic effects have been studied primarily with naturally generated hydrogen sulfide, that is with bacteria or geothermally produced gas. Ambient levels generated by anthropogenic sources are well below those known to cause symptoms of injury to higher plants. Hydrogen sulfide can act as a nutrient sulfur source in plants that are sulfur-deficient. H_2S in water, generated through decay, can be damaging to plants such as rice. Aquatic animals such as fish can be injured by high sulfide levels. The toxicity is similar to that shown in mammals, including humans. Effects on wildlife have not been demonstrated from ambient H_2S levels, although high levels from accidental releases can be lethal.

1.2 METABOLISM AND TOXICITY

Hydrogen sulfide (H_2S) is an extremely hazardous gas. According to the National Institute of Occupational Safety and Health (NIOSH), it is the leading cause of sudden death in the workplace. Its mechanism of cellular toxicity is like that of cyanide but more potent.

The immediate effect of inhalation of 1000 to 2000 ppm or more of H_2S is respiratory paralysis leading to death after a breath or two, due to inhibition of the respiratory center of the brain. At concentrations of 500 to 1000 ppm, respiratory paralysis is preceded by a period of rapid breathing or hyperpnea, and death will result unless the victim is removed from exposure and artificially ventilated.

At concentrations between 250 and 500 ppm, the gas is extremely irritating to the mucous membranes of the respiratory tract and of the eyes. Pulmonary edema, which can be life-threatening, almost always occurs. Extended exposure to the gas at concentrations above 50 ppm can result in pulmonary edema, although dryness and inflammation of the epithelia of the entire respiratory tract are more common. The epithelia of the eye, especially of the conjunctiva and the cornea, are similarly affected, resulting in "sore eye" or "gas eye." This is characterized by inflammation, lacrimation, and mucopurulent exudate,

with permanent scarring of the cornea occurring after ulceration, in some cases.

It is a fallacy to assume that the obnoxious odor of H_2S (like that of rotten eggs) would give warning of the presence of the gas, except at low concentrations. The odor threshold in humans is low--0.1 to 0.2 ppm--but at levels of 150 to 250 ppm, the olfactory sense is lost. Those recovering from potentially lethal exposures recall either no smell at all or a "sweetish" smell before losing consciousness. Pain from the irritant effect, especially in the eyes, also warns of dangerous exposure insufficiently, since the gas anesthetizes the nerve endings in these mucous membranes.

The levels of gas that produce these severe effects have generally not been encountered in the ambient air or even in the workplace. Limited ambient air monitoring data for various U.S. geographic locations, obtained prior to 1965, indicated maximum concentrations of less than one ppm (1.4 mg/m^3) (see Table 2-2). Routine measurements of the concentration of hydrogen sulfide in ambient air were not made by the National Air Sampling Network, and more recent monitoring information does not exist in the published literature, which could aid in establishing current ambient exposure levels.

It is only during catastrophic releases or failures of containment processes that the public is exposed to high concentrations of gas ($\geq$50 ppm) that have been associated with chronic or acute pathological changes. However, during such accidents, there is often loss of life. Such an accident occurred in 1950 at Poza Rica, Mexico, when a flare burning off H_2S at a natural gas desulfurization plant failed. The nearby community was inundated with gas for 20 minutes. As a result, 320 people were hospitalized, of whom 22 died. After the Lodgepole gas well blowout, ambient exposure levels of gas reached 15 ppm, and there were complaints of eye and respiratory irritation from the exposed population. No long-term effects were recorded and affected people and animals recovered completely.

Hydrogen sulfide is not considered to be a cumulative poison, since it is fairly rapidly oxidized to sulfates and excreted by the kidneys. Physicians reporting on recovered victims indicate that neurological and cardiologic lesions persist after high-level exposure, but no clear-cut sulfide toxicity has been implicated. The damage has not been differentiated from that which occurs as a result of anoxia or ischemia of brain or heart. While there are also clear indications of damage to the eighth cranial nerve and its associated

CNS connections, manifested as disturbances in balance and gait, this too may be the result of anoxia rather than specific sulfide toxicity.

There are no data regarding long-term exposure to low-level concentrations of H_2S. Those effects that have been attributed to such exposure, such as headache, fatigue, dizziness, irritability, and loss of libido, may result from long-term low-level exposure (less than 10 ppm), to gas but could also result from a single, high-level exposure, or recurring high-level exposures. Other workplace effects such as high humidity, temperatures, noise levels, and work-shift effects have not been ruled out. Unfortunately there are insufficient data to establish a no-observed-effect level (NOEL) or lowest-observed-effect level (LOEL) for such exposures. Sufficient data are also lacking to unequivocally state that mutagenic, carcinogenic, teratogenic, or reproductive effects do not occur.

1.3 RECOMMENDATIONS

False assumptions about recognition of danger by odor need to be dispelled and adequate information for dealing with catastrophic accidents needs to be promulgated. The need to remove victims from exposure and to assist ventilation must be made clear. Rescue workers must know that self-contained breathing apparatus is absolutely required if contaminated areas are to be entered. Potential rescuers have died together with victims who could have been saved because they were not aware of the lethality and rapid, overwhelming action of hydrogen sulfide.

There is a clear need for epidemiologic studies of long-term, low-level exposures of populations near or involved in industries producing H_2S. Studies that resolve questions of genotoxicity and carcinogenicity also need to be performed, and reproductive effects in animals need to be evaluated.

2. PHYSICAL AND CHEMICAL PROPERTIES

Hydrogen sulfide (H_2S) is a colorless gas, heavier than air under conditions of standard temperature and pressure (specific gravity = 1.192), with a characteristic offensive odor, like that of rotten eggs, at low concentrations. Its molecular weight is 34.08 (Weast, 1982). It is flammable in air and burns with a pale blue flame. Its auto-ignition temperature is 260°C, with explosive limits of 4.3 and 46 percent by volume. The gas has flammability limits from 44 percent to 4.0 percent (National Fire Protection Association, 1978). It may be ignited by static discharge (Manufacturing Chemists Association, 1968). Its combustion products are water and sulfur dioxide (Compressed Gas Association, 1981). Hydrogen sulfide is soluble in water (437 mL/100 mL at 0°C, and 186 mL/100 mL at 40°C) (Weast, 1982), which may be important from a health viewpoint. It is also soluble in ethanol, carbon disulfide (Weast, 1982) and a number of other organic solvents including ether, glycerol, and solution of amines, alkali carbonates, bicarbonates, and hydrosulfides (National Research Council, 1977). The vapor pressure of hydrogen sulfide is 18.75×10^5 Pa at 20°C and 23.9×10^5 Pa at 30°C. Its melting point is -85.5°C and its boiling point is -60.3°C (Macaluso, 1969).

Hydrogen sulfide can be oxidized by a number of oxidizing agents. The type of reaction and its rate are dependent on the nature and type of the oxidizing agent involved. Principal products of these reactions are sulfur dioxide, sulfuric acid, and elemental sulfur. Reaction with oxides of nitrogen in the atmosphere can result in the formation of sulfur dioxide (SO_2) and/or sulfuric acid (H_2SO_4); in water the primary product is elemental sulfur. Interaction with photochemically produced oxidants and OH radicals and ozone produces SO_2, with further oxidation eventually producing sulfuric acid and/or sulfate ion (SO_4^+).

Hydrogen sulfide is the only thermodynamically stable binary sulfur-hydrogen compound that occurs frequently in nature. It is the sulfur analogue to water. Because of the relative lack of hydrogen bonding, it exists as a gas

under normal conditions. However, it is easily liquefied by reduced temperature or increased pressure. The liquid is colorless, with a viscosity one-hundredth that of water (Bailar et al., 1973).

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3. MEASUREMENT AND ANALYSIS

There exist a number of sampling and analytical techniques for hydrogen sulfide which are used in measurement of ambient air concentrations and in industrial hygiene. Samples may be taken intermittently or continuously. Analytical techniques include iodometric titration, used in industry, with an accuracy limit of ~0.70 mg/m^3 (0.50 ppm) per 30 liters of air sampled, and chemical reaction with N,N-dimethyl-p-phenylenediamine and ferric chloride to form methylene blue, which can be spectrophotometrically measured for H_2S in concentrations from 0.001 to 0.1 mg/m^3 air (more concentrated samples must be diluted). This latter method is considered the most accurate means of determining H_2S in air and water (National Research Council of Canada, 1981). There is a standard method for the determination of hydrogen sulfide and mercaptan sulfur in natural gas over the range 0 to 11 mg/m^3 (American Society for Testing and Materials, 1981).

There is a standard reference method for ambient testing for hydrogen sulfide. This method may be used to determine concentrations of hydrogen sulfide at ambient levels below 1 µg/m^3 without preconcentration. It uses gas chromatography with a photoionization detector (Environmental Protection Service, 1984) (Canada). Low concentrations in ambient air are measured in field samples using paper or tiles impregnated with lead acetate, which darkens with exposure. The range of concentrations detectable is ~0.15 to ~1.5 mg/m^3. The color of the exposed samplers fades with exposure to turbulent air and light. Use of lead acetate filter tape in continuous volume air samplers is questionable because of fading that is due not only to interaction with light but exposure to any oxidant (Sanderson et al., 1966). Tapes impregnated with mercuric chloride do not fade (Paré, 1966), but sulfur dioxide in the air may change its sensitivity to H_2S (Dubois and Monkman, 1966).

A combination of gas chromatographic analysis and flame photometer detection is a dynamic system for sampling sulfur-containing gases, including H_2S in ambient air. The system's sensitivity depends on a number of variables, including the materials of which the sampler is made and the handling of the

sample as it goes through the gas chromatograph. Its detection range is 0.005 to 0.13 mg/m^3 (Pecsar and Hartmann, 1971).

Oehme and Wyden (1966) developed a method with a detection range of 0.7 to 70 mg/m^3 (0.5 to 50 ppm) for the electrochemical determination of hydrogen sulfide in air. This technique uses a silver rod coated with silver sulfide as an indicating ion electrode. The method was improved in 1975 (Kruszyna et al., 1975).

Adams and Koppe (1967) developed a technique using a gas chromatograph coupled with a microcoulometric bromine filtration cell to determine hydrogen sulfide emitted into the air from kraft paper mills. Concentrations down to a lower limit of 0.015 mg/m^3 can be measured on electronic titration equipment developed by Thoen et al. (1968).

Concentrations of 50 to 1000 ppb of H_2S in air can be determined by trapping the gas in an aqueous sodium hydroxide solution, using an ascorbic acid absorber, and titrating the resulting sulfide ion with a standard cadmium sulfide solution and a sulfide ion-selective electrode as an indicator (Ehman, 1976).

The most sensitive analytic method was reported by Natusch et al. (1972). It is a fluorescence method with a sensitivity of 0.0000002 mg/m^3 hydrogen sulfide.

There is also a standard method for the determination of hydrogen sulfide and sulfur dioxide in industrial aromatic hydrocarbons (American Society for Testing and Materials, 1982).

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4. SOURCES

4.1 NATURAL OCCURRENCE

Hydrogen sulfide is produced in nature primarily through the decomposition of organic material by bacteria. It develops in stagnant water that is low in oxygen content, such as bogs, swamps, and polluted water (Denmead, 1962; Dixon and Lodge, 1965; Alexander, 1974). The gas also occurs as a natural constituent of natural gas, petroleum, sulfur deposits, volcanic gases and sulfur springs. Natural sources constitute approximately 90 percent of the atmospheric burden of hydrogen sulfide. This has been estimated to be 90 to 100 million tons, of which 60 to 80 million are produced annually from land sources and approximately 30 million tons from aquatic areas (Urone, 1976).

4.2 PRODUCTION SOURCES

Industrial processes and other anthropogenic sources contribute approximately ten percent of the air burden of hydrogen sulfide. The National Institute for Occupational Safety and Health (1977) lists 73 industries that emit H_2S (see Table 4-1). The gas is used mainly as an intermediate and reagent in the preparation of other compounds of reduced sulfur. Kraft paper mills and manufacturers of viscose rayon and polyethylene and polyester resins use it, and processing releases H_2S to the air. Petroleum refineries, natural gas plants, petrochemical plants, coke oven plants, iron smelters, food processing plants, tanneries, heavy water processing plants, and a variety of metal alloy manufacturers release hydrogen sulfide as a by-product. Hydrogen sulfide found in natural gas may be present in ranges from 1.5 to 90 percent. It must be removed prior to use of the natural gas for heating or power production. It is an important source of elemental sulfur. Natural gas is usually sold only when H_2S content is less than 23 mg/m^3 (<16.4 ppm), but some of the H_2S does escape during transport and processing of natural gas (Miner, 1969). Processing of high-sulfur coal and oil can also result in the release of hydrogen sulfide. Crude oil stock of 20,000 barrels may form up to 50 tons of H_2S (Miner, 1969).

TABLE 4-1. OCCUPATIONS WITH POTENTIAL EXPOSURE TO HYDROGEN SULFIDE

Animal fat and oil processors	Lead removers
Animal manure removers	Lithographers
Artificial-flavor makers	Lithopone makers
Asphalt storage workers	Livestock farmers
Barium carbonate makers	Manhole and trench workers
Barium salt makers	Metallurgists
Blast furnace workers	Miners
Brewery workers	Natural gas production and processing workers
Bromide-brine workers	Painters using polysulfide caulking compounds
Cable splicers	Papermakers
Caisson workers	Petroleum production and refinery workers
Carbon disulfide makers	Phosphate purifiers
Cellophane makers	Photoengravers
Chemical laboratory workers, teachers, students	Pipeline maintenance workers
Cistern cleaners	Pyrite burners
Citrus root fumigators	Rayon makers
Coal gasification workers	Refrigerant makers
Coke oven workers	Rubber and plastics processors
Copper-ore sulfidizers	Septic tank cleaners
Depilatory makers	Sewage treatment plant workers
Dyemakers	Sewer workers
Excavators	Sheepdippers
Felt makers	Silk makers
Fermentation process workers	Slaughterhouse workers
Fertilizer makers	Smelting workers
Fishing and fish-processing workers	Soapmakers
Fur dressers	Sugar beet and cane processors
Geothermal-power drilling and production workers	Sulfur spa workers
Gluemakers	Sulfur products processors
Gold-ore workers	Synthetic-fiber makers
Heavy-metal precipitators	Tank gagers
Heavy-water manufacturers	Tannery workers
Hydrochloric acid purifiers	Textiles printers
Hydrogen sulfide production and sales workers	Thiophene makers
Landfill workers	Tunnel workers
Lead ore sulfidizers	Well diggers and cleaners
	Wool pullers

Source: National Institute for Occupational Safety and Health (1977).

Combustion of sulfur-contaminated fuels releases some H_2S to the atmosphere, a problem which industries have generally mitigated by both decreasing the sulfur content of fuels and by catalytically oxidizing the hydrogen sulfide. In automobiles, the latter method is used, but is circumvented when carburetors and/or catalytic converters are not functioning properly. Agriculture, too, is a source of hydrogen sulfide, particularly in large feed-lot or barn operations, where bacteria produce the gas in manure piles and tanks, and in settling ponds. Some fatal cases of H_2S poisoning have occurred in connection with the processing of manure and with work associated with human sewage treatment and latrines. Deaths have been reported in pigs and cattle following the emptying of slurry (manure) tanks, when agitation releases toxic gases (Clarke and Clarke, 1975; Lawson and McAllister, 1966; McAllister and McQuitty, 1965).

Most cases of acute toxicity occur in accidental or episodic releases associated with leaks from storage tanks or processing equipment, or in transfer or transport of the gas or mixtures containing the gas. (See Chapter 8: Toxicity).

4.3 ATMOSPHERIC TRANSPORT AND ENVIRONMENTAL FATE

Studies of photo-oxidation by Cox and Sandalls (1974) concluded that free radicals such as ·O and ·OH generated photochemically were of importance in oxidizing H_2S. Stuhl (1974) suggested that such oxidations were an important atmospheric process. Rate constants for the reaction of H_2S with OH radicals, ranging from $<10^{-13}$ to 10^{-10} cm^3 $mole^{-1}s^{-1}$, were used to derive a lifetime for H_2S in the troposphere ranging from 12 to 27 hours (Sprung, 1977; Eggleton and Cox, 1978; Wine et al., 1981; Servant and Delaport, 1982). Robinson and Robbins (1970), using data from other researchers, estimated that the surface-catalyzed reactions of H_2S with O_3 are fast enough to cause H_2S to have a mean residence time in the troposphere from two hours in urban areas to about two days in more remote, unpolluted areas. However, more recent studies by Hales et al. (1974) suggest such catalysis is negligible. Spedding and Cope (1984) carried out a limited number of experiments at ground level in a geothermal plume, in both summer and winter, and concluded that atmospheric lifetimes of H_2S oxidation to SO_2 were less than those deduced in the laboratory reactions of H_2S with OH radicals. They proposed that at least one other mechanism which occurs

in the dark when OH radicals are not present is responsible for H_2S oxidation. Their calculated lifetime for H_2S in air was about ten hours.

Studies by Becker et al. (1975) and Hales et al. (1974) show that homogeneous reactions of H_2S with O_3 are very slow, and can be considered negligible when compared to reaction with ·OH (Sprung, 1977). Becker et al. (1975) calculated the rate constants for the hypothetical bimolecular reaction

$$H_2S + O_3 \rightarrow \text{products}$$

at $k_1 = < 2 \times 10^{-20}$ cm^3 $molec^{-1}s^{-1}$. The authors state: "This number reflects the technically limited accuracy in measuring slow reaction rates at sufficiently low reactant concentrations to exclude chain processes rather than a true biomolecular rate constant k, which may still be substantially lower."

The lifetime of H_2S is affected by ambient temperature and other atmospheric variables including humidity, sunshine, and presence of other pollutants. The decreased temperatures and decreased levels of ·OH in northern regions (e.g. Alberta, Canada) in winter increase the residence time of H_2S in air (Bottenheim and Strausz, 1980).

Microorganisms in soil and water are involved in oxidation-reduction reactions which oxidize hydrogen sulfide to elemental sulfur (see Chapter 5). Members of the genera Beggiatoa, Thioploca, and Thiotrix function in transition zones between aerobic and anaerobic conditions where both molecular oxygen and hydrogen sulfide are found (National Research Council, 1977). Joshi and Hollis (1977) described how Beggiatoa protects rice plants from the inhibitory effects of H_2S that accumulates in the soil (see Chapter 5). Other genera such as Thiobacterium, Macromonas, Thiovulum and Thiospira also interact at interfaces of water containing oxygen and water containing H_2S, but since these organisms have not been isolated in pure culture, their specific role is less well understood. Some photosynthetic bacteria oxidize hydrogen sulfide to elemental sulfur. Members of the families Chlorobiaceae and Chromatiaceae (purple sulfur bacteria) are obligate aerobes and are phototropic, and are found in waters with high H_2S concentrations (National Research Council, 1977). The interactions of these organisms form part of the global sulfur cycle, which is diagrammed in Figure 4-1.

Hydrogen sulfide is oxidized by microbes to elemental sulfur, and finally to sulfate, which is chemically relatively stable. Sulfate can be taken up by

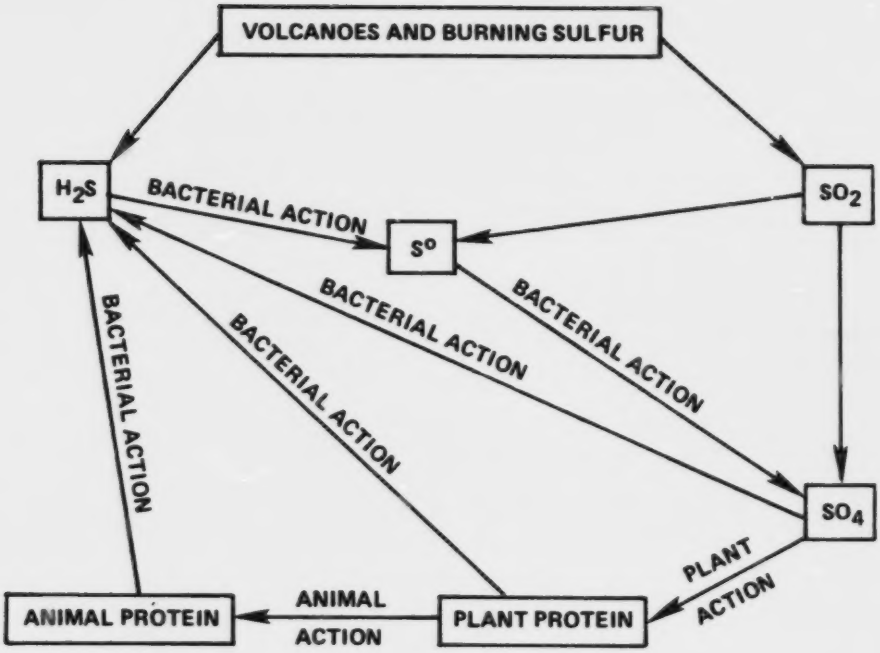

Figure 4-1. The sulfur cycle.

Source: National Research Council (1977).

Figure 4-1. The sulfur cycle (National Research Council, 1977)

plants and incorporated into plant protein, which in turn is incorporated into animal protein by herbivorous animals, and on through the food web by carnivores. Decay of plant and animal material releases hydrogen sulfide again through the action of decay microorganisms; some strictly anaerobic sulfate-reducing bacteria can also reduce sulfate directly to H_2S.

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5. ECOLOGICAL EFFECTS

5.1 INTRODUCTION

Much of the work done with ecological effects of hydrogen sulfide relates more directly to bacteriologically or geothermally produced gas than it does to anthropogenic sources. Hence, more information is available about effects on plants and animals in contact with H_2S through soil and water than through air.

5.2 EFFECTS ON HIGHER PLANTS

Ambient levels of H_2S are well below those known to cause symptoms of injury to higher plants (National Research Council, Canada, 1977). Field injury of plants has not generally been reported from ambient exposures. A report from a gas well blowout in Alberta, Canada, in which hydrogen sulfide concentrations were monitored in the 5- to 10-ppm range for some hours, with higher peak exposures, indicated the possibility of an effect on vegetation. Alfalfa and hay crops in the exposure area after the Lodgepole blow-out were reported as low as one-half to one-third normal yield. No comparisons with unexposed croplands were made, and the effect of seasonal parameters such as moisture and temperature was not ruled out. It must be noted that the blowout occurred in winter so no growing field crops were affected. There were reports that house plants died during the blowout (Lodgepole Blowout Inquiry Panel, 1984).

Relatively few air exposure or fumigation experiments have been done with higher plants. McCallan et al. (1936) and Benedict and Breen (1955) conducted short-term, high-exposure fumigation studies on 29 species of vegetation and 10 weed species, respectively. In McCallan's study, plants were exposed for 5 hours in the middle of the day to concentrations ranging from 20 to 400 ppm (28 to 560 mg/m^3) H_2S. A wide range of injury was seen, with eight species showing no injury at 400 ppm, while other species displayed visible injury at less than 40 ppm. Young, growing tissues were most susceptible to injury.

Benedict and Breen (1955) fumigated with 100 to 500 ppm H_2S for four hours 10 species of weeds 3 to 6 weeks of age. They also observed species differences in susceptibility to injury and noted that younger plants were more sensitive to damage than older ones. Both studies indicated that increases in temperature exacerbated the damage, as did dry soil.

Heck et al. (1970) describe the damage to young shoots and leaves as a scorching, with basal and marginal scorching also of the next oldest leaves. Mature leaves are unaffected. Heck et al. (1970) provided a table which divides 38 selected plants into sensitive, intermediate and resistant groupings. Included among plants sensitive to H_2S are kidney bean (Phaseolus vulgaris L.), buckwheat (Fagopyrum esculentum Moench), clover (Trifolium sp.), cucumber (Cucumis sativus L.), soybean, (Glycine max. Merr.), tobacco (Nicotiana glauca Grah. and Nicotiana tabacum L.), and tomato (Lycopersicon esculentum Mill.). Among intermediately sensitive plants are Kentucky blue grass (Poa pratensis L.), pepper (Cupisium futescens L.) and rose (Rosa sp.). Plants resistant to the effects of H_2S are apple (Malus pumila Mill.), cherry (Prunus serotina Ehrhe.), mustard (Brassica campestris L.) and strawberry (Fragaria sp.), among others.

Thompson and Kats (1978) fumigated various crop and forest plants in continuous, long-term exposure experiments. Two procedures, one using concentrations of 0, 0.03, 3.0 and 30 ppm, the other using 0, 0.03, 1.0 and 3.0 ppm were employed. (1.4 x ppm = mg/m^3). In contrast to the low sensitivity to H_2S shown by plants in the high concentration, short-term exposures conducted by McCallan et al. (1936) and Benedict and Breen (1955), plants exposed to very low concentrations of H_2S over long periods of time showed considerably more damage (Thompson and Kats, 1978). For instance, alfalfa (Medicago sativa L.) suffered visible leaf lesions after five days exposure to 3 ppm H_2S (4.2 mg/m^3) but no damage was seen at 0.03 ppm. Yield of alfalfa, which is normally cut and regrown in farming practice, was reduced at 3 ppm and 0.3 ppm, but not at 0.03 ppm. Seedless grapes (Vitis vinifera L.) suffered severe damage at 3 ppm and easily detectable damage at 0.3 ppm. Ponderosa pine (Pinus ponderosa) showed no visible effect until 4 to 6 weeks of exposure at 3 ppm, with defoliation at 8 weeks. At 0.3 ppm, tip burn occurred after 8 weeks. No effect was seen at 0.03 ppm. The exposed plants accumulated sulfur in leaves, although pine did less than alfalfa or grape, perhaps because of lower normal growth rates.

California buckeye (Aesculus california), sugar beet (Beta vulgaris) and lettuce (Lactuca sativa) were resistant to damage, and actually the latter two species exhibited considerable stimulation to growth at lower (0.3 ppm) H_2S concentration. It was indicated in repeat experiments that temperature variation might play a role in differential growth rates.

Airborne sulfur dioxide has been shown to contribute to the nutrition of plants, especially those grown in sulfur-deficient soils. Faller and Linser (1972), using hydrogen sulfide in addition to sulfur dioxide, confirmed the findings of earlier researchers regarding this phenomenon. In the H_2S experiments Faller and Linser exposed mature, flowering and viable seed-bearing sunflowers growing in sulfur-free nutrient solution to three weeks of H_2S fumigation ranging from "a few" ppm to more generally 200 ppm. Growth of all parts of the plants was stimulated very significantly over that of the sulfur-deficient controls, the stem alone approximately doubling in height. Sulfur content in all plants was elevated above that of controls, including the roots, which result has not been found in nutrient experiments with SO_2.

Gas uptake in plants occurs primarily through stomata, which can be opened or closed in response to changes in environmental conditions such as illumination, humidity, and perhaps pollutant concentrations. The cell surface available for gas exchange within leaves can be considerably larger than the external leaf surface, which is covered with cuticle and therefore is not permeable to gas. For example, the lilac leaf has 6 to 8 times the external surface internally, while the bluegreen eucalyptus has 31.3 times the surface area internally (Turrell, 1936). Closure of stomata can therefore reduce gaseous uptake dramatically and perhaps protect against short-term, high-level exposure (Hosker and Lindberg, 1982). Conversely, stomatal opening can increase gas uptake, which may constitute a nutrient effect.

Closure of stomata in response to air pollution ("smog") was observed by Mansfield and Heath (1963). Sulfur dioxide, in concentrations as low as 0.07 mg/m^3, decrease stomatal resistance (indicating opening of stomata) but higher concentrations do not cause a corresponding decrease in resistance, as is the case with CO_2 (Biscoe et al., 1973). An effect on stomatal opening or closing has not been investigated with H_2S. Taylor et al. (1983) measured flux of sulfur-containing gases to vegetation, however. Using bush bean (Phaseolus vulgaris) and soybean (Glycine max), they showed that internal flux, through stomata, was less for H_2S than sulfur dioxide (SO_2) but greater for H_2S than

carbonyl sulfide (COS), methyl mercaptan (CH_3SH) or carbon disulfide (CS_2). No direct effect on stomatal function could be deduced from these experiments.

Uptake of sulfide from soil and water has been studied far more extensively than air uptake, since this can represent plant toxicity in soils that are waterlogged, or for plants raised in water, as rice is. The sulfide found in soils and water results more from bacterial action during decay, mostly of plant and animal protein, than it does from any anthropogenic source of air pollution. Ford (1973) reported that citrus trees in poorly drained areas of Florida suffered root injury at a threshold concentration of 2.8 mg/liter aqueous sulfide concentration, after 5 days exposure. Several investigators have examined the effect of disulfide on rice (Oryza sativa L.). Hollis and his co-workers (Allam and Hollis, 1972; Joshi and Hollis, 1977; Joshi et al., 1975; Pitts et al., 1972) found that 1 mg/liter of sulfide inhibited nutrient uptake, oxygen release, and phosphate uptake by rice seedlings. Some varieties, however, showed enhanced nutrient uptake with exposure to 0.05 mg/liter of sulfide. It was learned that presence in the soil of the bacterium Beggiatoa prevented the toxic effect of H_2S, while the rice seedlings' presence symbiotically enhanced the survival of the bacterium. Beggiatoa oxidizes hydrogen sulfide (Joshi and Hollis, 1977). Respiration in rice roots was investigated by Allam and Hollis (1972). Increasing hydrogen sulfide concentrations were found to increasingly inhibit respiration, so that 0.1 mg/liter inhibited respiration 14 percent, while 3.2 mg/liter inhibited this function 25.6 percent. Assays of root homogenates were made after 3 to 6 hours of exposure to 0.1 to 3.2 mg/liter sulfide. Assayed enzymes that showed inhibition of respiration included ascorbic acid oxidase, polyphenol oxidase, catalase, peroxidase and cytochrome oxidase. Of these, cytochrome oxidase was most dramatically inhibited. Forty percent inhibition was measured after 6 hours root exposure to 0.1 mg/liter sulfide. This evidence is consistent with the known mode of toxicity of H_2S, which is inhibition of metal-containing enzymes, most specifically cytochrome oxidase, the final electron acceptor of the respiratory chain. When it is incapable of accepting electrons, electron transport along the entire cytochrome chain stops, halting oxidative respiration.

5.3 EFFECTS ON ALGAE AND BACTERIA

Other plant communities in the ecosystem are also affected by hydrogen sulfide in natural waters. Czurda (1941) found that some species and strains of algae were inhibited by 1 to 2 mg/liter sulfide, while others seemed unaffected at concentrations of 8 to 16 mg/liter. He found that effects on various physiologic functions such as cell division, respiration, uptake of nutrients and anaerobic respiration were variably affected in different species of algae. Nakamura (1938) delineated enzyme inhibition in two species of algae, Pinnularia sp, and Oscillatoria sp. Concentrations of sulfide of 0.1 mM (3.2 mg/liter) completely inhibited catalase in both species and stimulated oxygen uptake in darkness. Photosynthetic oxygen production was strongly inhibited even at 0.01 mM (0.32 mg/liter), while CO_2 fixation was unaffected. Cell division was slightly inhibited by 1.0 mM (32 mg/liter) in Oscillatoria, and was stimulated twofold in Pinnularia.

The role of bacteria in the sulfur cycle, both in the evolution of H_2S during decay processes and in the oxidation of sulfide to sulfate, is discussed in Chapter 4, Section 4.3, Atmospheric Transport and Fate.

5.4 EFFECTS ON AQUATIC ANIMALS

The effect of dissolved hydrogen sulfide gas and dissociated sulfide ion (HS^-) has been examined in a number of studies of aquatic organisms. Hydrogen sulfide is highly toxic to several fish species. Broderius and Smith (1976) reported the effect of H_2S, sulfide ion and pH variation on LC_{50} (lethal concentration$_{50}$) to the fathead minnow. Ninety-six-hour LC_{50} values for dissolved hydrogen sulfide gas (H_2S) decreased linearly from 57.3 µg/liter to 14.9 µg/liter, with pH increases ranging from 7.1 to 8.7. The more alkaline the pH, the more H_2S, which is a weak acid, dissociates. Undissociated H_2S is thought to be the primary toxic sulfur species which interacts with respiratory enzymes, so the increase in toxicity indicated by the decreased LC_{50} seems paradoxical. Ions are transported across membranes such as lung epithelia less readily than neutral chemical species. However, transport across the gill surface of fish involves a complex ion exchange mechanism for ridding fish blood of CO_2 in the form of bicarbonate ion (HCO_3^-), formed through the action of the enzyme carbonic anhydrase, which is found in gill tissue. The authors (Broderius and Smith, 1976) suggest that acidic microenvironments at the gill surface may re-form the

undissociated H_2S, which is easily transported. It is equally plausible to assume that HS^- exchanges for HCO_3^- in the ion exchange, which normally involves chloride ion (Cl^-), and that the hydrogen ion (H^+) released from the cleavage of carbonic acid (H_2CO_3) by carbonic anhydrase associates with HS^- within the cell to re-form undissociated H_2S. The 96-hour LC_{50} values of dissolved sulfide ion increased linearly from 64.0 to 780.1 µg/liter with increasing pH ranging from 6.5 to 8.7. The data for the HS^- ion are straightforward: the more alkaline the pH, the more S^- ion forms, the lower the transport rate and the resulting toxicity.

Cleland and Kingsbury (1977) reported that the bluegill Lepomis macrochirus was adversely affected at H_2S concentrations of 1 µg/liter dissolved H_2S. A 96-hour exposure study of northern pike, Esox lucius, by the same authors, reported an LC_{50} ranging between 17 to 32 µg/liter H_2S. Walleye eggs (Stizostedion vitreum) would not hatch at concentrations of 0.02 to 0.7 µg/liter. Smith (1978) exposed several species of freshwater fish to low concentrations of H_2S and determined no-effect levels of ~5 µg/liter for all the exposed fish. Ninety-six-hour LC_{50} values for the various fish species ranged from 25 to 145 µg/liter. The author recommended a 2 µg/liter H_2S concentration as a safe limit for freshwater fish. Smith and Oseid (1972) also investigated H_2S effects on walleye eggs and fry in 96-hour exposure studies. The LC_{50} values they report are 74 to 87 µg/liter for eggs and 7 µg/liter for fry. Reynolds and Haines (1980) exposed newly hatched brown trout to H_2S in concentrations ranging from 2 to 13 µg/liter for periods of 8 to 22 days. In contrast to the damaging effect mentioned in other studies, these authors reported that the survival rate increased in fry exposed to concentrations of 2 to 5 µg/liter H_2S, and that the exposed group's growth was enhanced by 50 to 200 percent.

Colby and Smith (1967) investigated the effect of hydrogen sulfide generated by paper fiber sludge deposits ("mats") on the survival of walleye (Stizostedion vitreum vitreum Mitchill) eggs and fry, and on Gammarus pseudolinaeus in field and laboratory investigations. In the field studies, green eggs (36 and 48 hours post-fertilization) and eyed eggs (2 weeks post fertilization) were placed on paper fiber sludge mats (5 stations) and normal river bottom (three stations) in which pH, dissolved oxygen and dissolved sulfide varied. Exposure times for two separate experiments were 6 and 13 days, to 5,800 eggs and 3,300 eggs respectively. The later study was followed by a survival-through-hatching study on 14-day-old eggs. Lowest survival for

green eggs occurred where dissolved oxygen concentration dropped below 3.0 ppm and where dissolved sulfide reached a concentration of 0.58 ppm. Eyed eggs and sac-fry mortalities were 100 percent after 6 days at a highest dissolved sulfide concentration of 0.14 ppm. At 0.28 ppm all eyed eggs and sac fry died within 2 days. Green eggs (3 and 4 days old) showed greater tolerance to dissolved sulfide when oxygen concentrations in the water were higher. At 5.6 ppm dissolved oxygen, little mortality was noted at 0.08 and 0.20 ppm dissolved sulfide, while at 0.34 ppm 98 percent died after 6 days, and at 0.52 ppm 100 percent died within 72 hours. In contrast, at 8.3 ppm dissolved oxygen, up to 96 percent of eggs exposed to 0.09, 0.21 and 0.27 survived the experiment. At 0.47 ppm dissolved sulfide, mortality was 97 percent within five days. In laboratory investigations, gammarids (Gammarus pseudolimnaeus) were intolerant to dissolved sulfide concentrations of 0.16 to 0.36 ppm, especially at low dissolved oxygen concentrations (1.2 to 1.3 ppm). They were far more tolerant to similar sulfide concentrations when dissolved oxygen was 5.0 to 5.1 ppm.

Torrans and Clemens (1982) noted in their work with channel catfish (Ictalurus punctatus) that not only oxygen but temperature had an effect on hydrogen sulfide toxicity. They investigated possible reasons for mortality of catfish during harvesting, when the black, malodorous sediment of pond bottoms is disturbed (and hydrogen sulfide is released into the water). Harvesting also usually occurs in the summer, when water temperatures are higher and dissolved oxygen is lower, and when transport over distances exposes fish to heat. Torrans and Clemens (1982) specifically examined the effect of hydrogen sulfide exposure on physiologic parameters and on cytochrome oxidase in fish tissues in vivo and in vitro. (See Chapter 7, Section 7.2, Metabolism and Pharmacokinetics and Chapter 8, Section 8.1, Animal Effects). Exposure of fish to 0.5 mg/liter H_2S at 20°C resulted in hyperpnea, followed immediately by apnea. Cytochrome oxidase inhibition in vivo varied with the type of tissue. Channel catfish and fathead minnows (Pimephales promelas) exposed to 20 mg/liter total dissolved sulfide at 20°C, pH 8.0 (1.0 mg/liter H_2S) were removed from the solution when respiration ceased and their tissues assayed for cytochrome oxidase activity. For the fathead minnow, enzyme activity varied from control levels in the testes to 55 percent inhibition in the kidney. In the channel catfish the inhibition ranged from 28 percent for brain to 66 percent for heart. The enzyme in the gill was affected before the brain and inhibited to a greater extent. Blood lactic acid levels rose, indicating active anaerobic

metabolism. The time course for recovery from hydrogen sulfide poisoning was determined. The enzyme returned from a 50 percent inhibition to normal levels in 6 hours, after fish were returned to fresh water.

In subchronic toxicity studies with the amphipod crustacean Gammarus pseudolimnaeus (gammarids), the 96-hour LC_{50} was determined to be 20 µg/liter, while the maximum safe level determined for 65-, 95-, and 105- day exposures was 10 times less: 2 µg/liter (Oseid and Smith, 1974). Chronic studies on juvenile and adult bluegills (Lepomis macrochirus) demonstrated a no-effect level of 2 µg/liter H_2S, but minnows, suckers, amphipods and some aquatic insects did show toxic effects at levels slightly higher than this limit (Smith et al., 1976; Smith, 1978).

EPA proposed in 1972 that a water quality criterion for undissociated H_2S should be set at 2 µg/liter for fish and other aquatic life in both fresh and marine waters (Cleland and Kingsbury, 1977). The National Academy of Sciences-National Academy of Engineering, Environmental Studies Board had earlier recommended such a standard for fresh water organisms, but proposed 10 µg/liter as a standard for marine life.

Some animals living in environments high in hydrogen sulfide concentration, such as those near deep ocean volcanic fumaroles, have symbiotic bacteria that are able to oxidize H_2S, detoxifying it but also using it as a source of energy. Powell and Somero (1986) have established that at least one animal, the gutless clam (Solemya reidi), has within its gill tissue bacteria which oxidize H_2S and provide a reduced carbon source for the clam. The initial step or steps of sulfide oxidation occur in the animal tissues, however, and mitochondria isolated from both gill and symbiont-free foot tissue coupled the oxidation of sulfide to oxidative phosphorylation (ATP synthesis). This previously unknown phenomenon suggests that other animals may be capable of sulfide oxidation and use of sulfide as an inorganic energy source.

5.5 EFFECT ON WILDLIFE

Very few studies exist which attempt to measure natural or accidental exposure of wildlife to hydrogen sulfide, or to determine its effects. One investigation by Siegel et al. (1986) examined the ambient levels of H_2S at Sulphur Bay Wildlife area on Lake Rotorua, New Zealand. Shore and water birds here are exposed to H_2S of geothermal origin in concentrations of 0.125 to 3.90 ppm. The authors state that exposure of these birds is higher than would be

expected for humans at these concentrations because small birds have a higher oxygen utilization rate and therefore a higher ventilation rate than mammals of human size do. Their target organ dose would therefore be higher. Yet populations in this wildlife area have thrived, as indicated by the increasing number of nests found for several species in the preserve. No other parameters of exposure were measured on either a population or an individual level.

An attempt to determine the effect on wildlife of exposure to fumes from a gas well blowout in Alberta, Canada was made by the Canadian Wildlife Service (New Norway Scientific Committee, 1974). An overflight of the well and surrounding area the day of the mishap, which examined the lakes and larger sloughs for any evidence of dead or distressed waterfowl, and the areas between lakes, as well as draws and valleys for dead deer, found none. At the time of the blowout all young fowl had reached flying size, so both young and adults tending them could fly from the contaminated area. A next-day overflight in the downwind area showed no dead or distressed birds and the distribution and activity of all birds seen appeared normal. Measurements at two mobile sites were between < 0.1 to 0.5 ppm H_2S.

The gas well blowout that occurred at Lodgepole, Alberta, Canada, was investigated by a board of inquiry. During the blowout three moose and a raven were found dead near the well site. Cause of death was not established. Animal track surveys indicated that large ungulates such as elk were avoiding the immediate well-site area during the winter of the blowout, but that they moved in normal patterns throughout the nearby forested areas, conforming to those seen in surveys conducted in 1981. A small mammal survey conducted by Alberta Fish and Wildlife in the cleared and perimeter areas of the well-site determined a shift in species composition but no significant changes in numbers. Local residents said that birds and small wild mammals disappeared from the area following the blowout, and this was confirmed by a local veterinarian. Concentrations between 5 and 10 ppm H_2S were measured at various sites in the area, at times (Lodgepole Blowout Inquiry Panel, 1984).

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6. EXPOSURE TO HYDROGEN SULFIDE

6.1 INTRODUCTION

Hydrogen sulfide has become an increasing industrial hazard only in the last sixty years. It is now the leading cause of sudden death in the workplace. NIOSH lists 73 categories of workers with potential for exposure to H_2S. Among those with greatest likelihood of hazard are natural gas drillers, processors and producers, petroleum production and refinery workers, kraft pulp industry, coke oven, blast furnace, and smelter workers, coal gasification workers, heavy water manufacturers, synthetic fiber and rayon makers, pipeline maintenance workers, miners, livestock farmers and manure processors, sewage treatment plant workers, sugar beet processing workers, and tannery workers (National Institute for Occupational Safety and Health, 1977) (see Table 6-1).

Ambient concentrations of H_2S tend to be low, primarily constituting an odor nuisance. Occasionally populations around sulfide-producing industries have been exposed to concentrations ranging from those causing malaise to accidental releases which were lethal.

6.2 AMBIENT CONCENTRATIONS

Examples of average and maximum atmospheric concentrations of hydrogen sulfide found in various U.S. geographical locations before 1965 are listed in Table 6-1. No more recent data on ambient levels of H_2S in the U.S. are found in the published literature. Ambient levels of H_2S are not routinely measured. Motor vehicles, especially those whose carburetors and/or catalytic converters are functioning improperly, are one source of concern for contributing to the H_2S air burden. Table 6-2 gives three specific scenarios of H_2S concentrations contributed by vehicles including well-adjusted and malfunctioning carburetors and catalytic converters.

Elevated ambient concentrations in two recorded episodes, one in the Great Kanawha River Valley in West Virginia in 1950, and one in Terre Haute,

TABLE 6-1. ATMOSPHERIC HYDROGEN SULFIDE CONCENTRATIONS (mg/m^3)*

Location	Average	Maximum
New York City, NY		
1956-1961	0.001	0.013
1962	0.001	0.006
Elizabeth, NJ		
August-October, 1963	0.001	0.247
Hamilton Township, NJ		
May-October, 1962	0.001	0.049
Woodbridge Township, NJ		
April-May, 1961	0.001	0.305
Greater Johnstown Area, PA		
1963	0.003	0.210
Winston-Salem, NC		
November-December, 1962	0.003	0.011
Lewiston-Clarkston Area, North Lewiston, ID near pulp mill, 1962		0.037
Great Kanawha-River Valley Industrial Area		
February 1950-August 1951	0.003-0.092	0.410
Camas, WA		
1962	0.001	0.006
Santa Barbara, CA		1.4
1949-1954		
St. Louis, MO		
1964	0.002-0.006	0.094
Terre Haute, IN		
May-June, 1964		>0.460

Source: Miner (1969).

*(1.4 $mg/m^3 \cong 1$ ppm)

Indiana in 1964, were reported as 0.41 mg/m^3 and ~0.46 mg/m^3, respectively (West Virginia Department of Health, 1952; U.S. Public Health Service, 1964). General symptoms of malaise, irritability, headache, insomnia and nausea were reported by members of the exposed populations. It was not possible to determine whether

TABLE 6-2. AMBIENT AIR SCENARIOS: HYDROGEN SULFIDE CONCENTRATIONS (mg/m^3)

Scenario	Current fleet	Current Fleet 25% malfunction	Entire Fleet 3-way catalysts	Entire fleet 3-way catalyst 25% malfunction
Roadway Tunnel				
Typical	0.00003	0.00084	0.0003	0.00223
Severe	0.00009	0.00214	0.00077	0.00568
Expressway				
Typical	0.000004	0.0009	0.0003	0.00025
Severe	0.00002	0.00038	0.00014	0.00101
Close proximity	0.000003	0.00008	0.00003	0.00021
Street Canyon				
Typical	0.000001	0.00003	0.00001	0.00008
Severe	0.00001	0.00021	0.00008	0.00056

Source: Harvey (1983).

these effects were the result of psychological response to the obnoxious odor or represented other types of neurological effects.

During the Lodgepole oil well blowout in the foothills of Alberta in 1982, transient levels of H_2S up to 14.5 ppm were detected in communities 20 km distant from the site. The maximum concentration detected in the city of Edmonton, 130 km away, was 0.52 ppm, where the odor level was substantial even at concentrations well under the peak (Lodgepole Blowout Inquiry Panel, 1984). The general symptoms of malaise, irritability, headache, insomnia, and nausea, were reported by the residents in the Great Kanawha River Valley and in Terre Haute, and additional symptoms reflecting ocular and lower respiratory tract irritation by residents in the Alberta exposure. The significance of the latter complaints was strengthened by the observation of residents and a veterinarian that livestock and smaller animals also had ocular irritation, cough and anorexia. Since no formal medical studies were done utilizing control populations, it is not possible to determine the mechanism or mechanisms of the production of the complaints. However, both physical irritation and a psychological response to the obnoxious odor seem likely possibilities at higher and lower concentrations of the gas.

Rotorua, New Zealand, is a major recreational and sports center for travelers from all over the world. The proximity of the city to an active geothermal system is evident from the widespread use of this energy source and the

prevailing odor of hydrogen sulfide. Ambient concentrations have been measured in a range from 0.005 to 1.9 ppm. A preliminary study revealed no evidence of health impairment (Siegel et al., 1986).

No federal ambient air or emission standards for H_2S are presently in place in the United States. There is a de minimis value for hydrogen sulfide of 0.00004 $mg/m^3/hr$ average included in the Code of Federal Regulations for Prevention of Significant Deterioration of Air Quality. The total reduced sulfur (TRS) value under this regulation is 10 $\mu g/m^3/hr$ average (Code of Federal Regulations, 1983). Several states, however, have standards which are described in Table 6-3.

TABLE 6-3. AMBIENT AIR QUALITY STANDARDS FOR H_2S

State	Concentration (ppm)	Averaging Time
California	0.03	1 hour
Connecticut	0.2	8 hours
Kentucky	0.01	1 hour
Massachusetts	0.014	24 hours
Montana	0.03	30 minutes
Nevada	0.24	8 hours
New York	0.10	1 hour
Pennsylvania	0.10	1 hour
Texas	0.08	30 minutes
Virginia	0.16	24 hours

6.3 OCCUPATIONAL CONCENTRATIONS

Hydrogen sulfide has been cited as a potential hazard in 73 occupations in the United States alone, in which approximately 125,000 employees are subject to exposure (National Institute for Occupational Safety and Health, 1977) (Table 4-1). Low-level concentrations occur routinely in certain industries such as viscose rayon production, pulp processing, oil refining, and gas and oil well operation. In all such occupations, potentially hazardous gases such as carbon disulfide, mercaptans, sulfur dioxide, and diverse hydrocarbons form a mixture with hydrogen sulfide, and individual effects of these pollutants have been difficult to delineate. Information regarding effects from low concentration exposure is scant and is often confounded by the presence of other gases in the work environment.

In 1977 NIOSH recommended a ceiling limit of 15 mg/m^3 or approximately 10 ppm H_2S for 10 minutes, for up to a 10-hour work shift in a 40-hour work week. The present threshold limit value (TLV)^{TM} for H_2S, expressed as a time-weighted average (TWA), is 10 ppm (~14 mg/m^3). (Threshold Limit Value^{TM} is set by the American Council of Governmental Industrial Hygienists for an 8 hr/day, 40 hr/week exposure of healthy workers). The TLV for short-term exposure limit (STEL), which represents the maximal concentration to which workers may be exposed for up to 15 minutes, is 15 ppm (~21 mg/m^3). Accidental exposure of workers and the general population have occurred in which the levels were much higher, sometimes by several orders of magnitude. For example in Poza Rica, Mexico, in 1950, an accidental release of hydrogen sulfide from an absorption unit in a natural gas refining plant killed 22 people and hospitalized 320 more in the nearby community, even though the release lasted only 20 to 25 minutes (McCabe and Clayton, 1952).

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7. METABOLIC FATE AND DISPOSITION

7.1 ABSORPTION

The most common route of entry for hydrogen sulfide is the lung. Experimentally, sodium sulfide (Na_2S) has been injected intravascularly or intraperitoneally, or instilled orally by gavage, so that its distribution and fate in tissues, as well as its metabolism, could be elucidated. Absorption of H_2S through the skin is limited. Exposure of large areas of skin of guinea pigs to pure H_2S was lethal after 45 minutes but did not affect dogs (Walton and Witherspoon, 1925). Exposure of the entire body, except the head, of rabbits allowed a qualitative detection of H_2S in expired air (Laug and Draize, 1942). Absorption through the tympanic membrane of workers wearing respirators was not a significant route of toxicity (Ronk and White, 1985).

In aqueous solution, for instance in body fluids, hydrogen sulfide has two acid dissociation constants and can thus exist as the hydrosulfide anion (HS^-) and as the sulfide anion ($S^=$). The pKa for step one is 7.04; for step two

$$H_2S \underset{(1)}{\rightleftharpoons} H^+ + HS^- \underset{(2)}{\rightleftharpoons} H^+ + S^=$$

the pKa is 11.96 (in solutions 0.01N to 0.1N @ 18°C). At human physiologic pH and temperature of 7.4 and 37°C respectively, about one-third of the total sulfide exists as undissociated H_2S, about two-thirds as HS^-, and minuscule amounts as $S^=$. Since unionized small molecules tend to diffuse across membranes more readily than ionized molecules do, it is likely that H_2S is absorbed more rapidly than the negatively charged ions. Absorption of H_2S in protozoans occurred more rapidly than the ionic species (Beerman, 1924). Absorption of H_2S from the peritoneal cavity of mice occurred more rapidly with an acidic carrier, which prevented sulfide ion formation, than in an alkaline carrier, which enhanced ion formation (Smith and Abbanat, 1966).

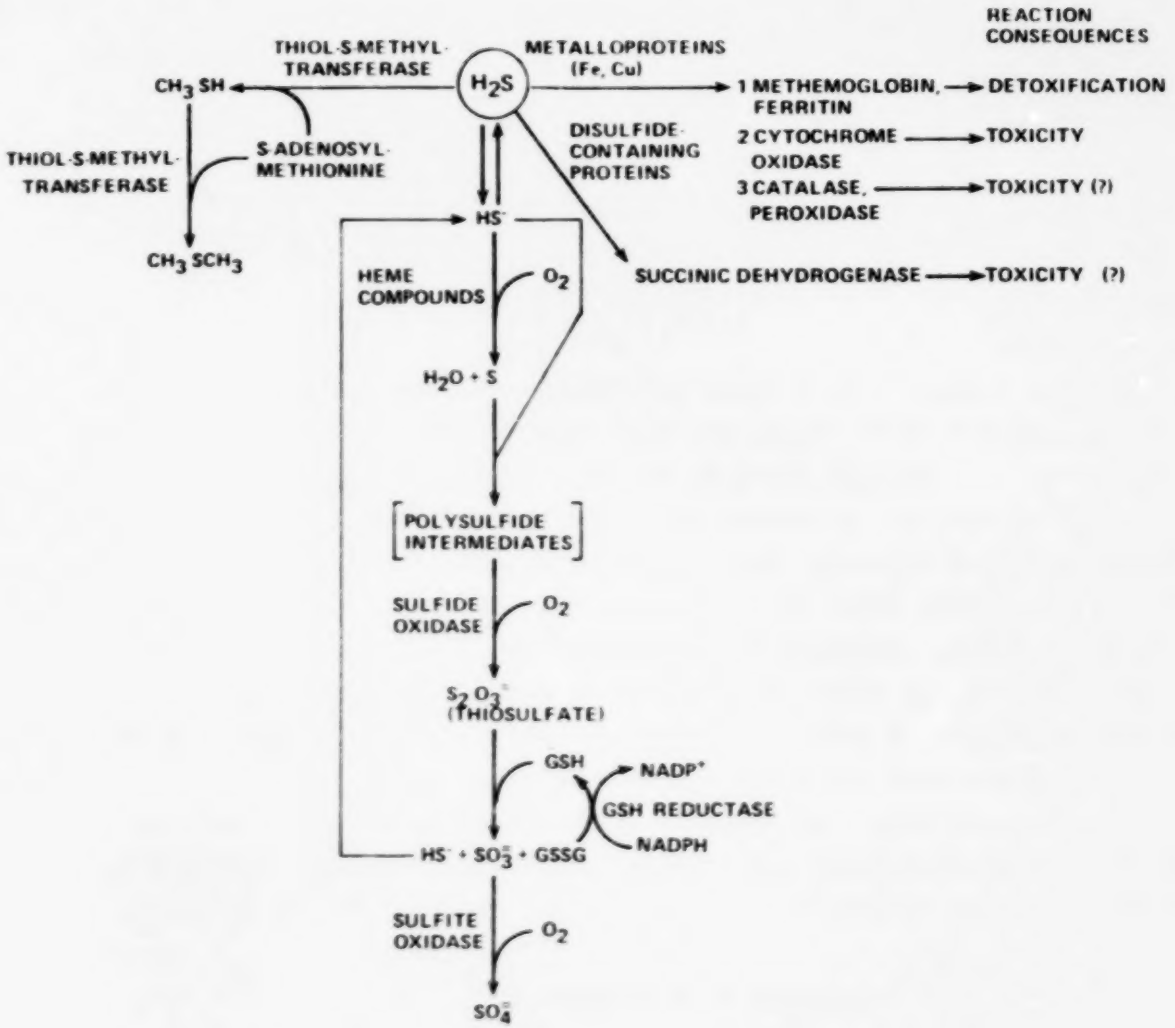

Figure 7-1. Metabolism of hydrogen sulfide.

Source: Beauchamp et al. (1984).

7.2 METABOLISM AND PHARMACOKINETICS

The metabolism of hydrogen sulfide can be divided into three pathways (Figure 7-1): (a) oxidation to sulfate, (b) methylation, and (c) reaction with metallic ion or disulfide-containing proteins (Beauchamp et al., 1984). Oxidation and methylation represent means of detoxification, while the interaction with essential proteins, particularly the iron-containing proteins of the respiratory chain, is largely responsible for the toxic actions of the gas.

The oxidation of sulfide to sulfate has been studied for nearly forty years and is as yet not precisely defined. While early *in vitro* studies with liver and kidney preparations postulated intermediates such as free sulfur, polythionates, and thiosulfate, Der-Garabedian (1945a,b) proposed that sulfide oxidase enzymatically catalyzed the oxidation of sulfide. Baxter et al. (1958) and Baxter and van Reen (1958) confirmed the existence of a liver sulfite oxidase.

The observation was made by Sörbo (1958) that heme catalyzed sulfide oxidation to thiosulfate. Several studies were initiated to determine the precise site of sulfide oxidation. ^{35}S-sodium sulfide incubated *in vitro* with blood rapidly bound to blood proteins (Curtis et al., 1972). It was demonstrated too that this was a route of oxidation which worked very slowly and was insufficient to account for very much sulfate formation in living systems. Other *in vitro* experiments (Bartholomew et al., 1980) showed that thiosulfate was the major oxidation product of sulfide in liver mitochondria, and that this could then be converted to sulfate by sulfite oxidase, which has been purified from rat and dog liver and kidney (MacLeod et al., 1961a,b). The precise locality for major oxidation of sulfite *in vivo* has not been unequivocally established, but the liver is the most probable site.

The lung participates little in metabolism of sulfide to sulfate. Using whole-body autoradiography after intraperitoneal injection or gavage instillation of ^{35}S-sulfide, Curtis et al. (1972) showed that while the lung accumulated ^{35}S-sulfide, very little was converted to radioactively labeled sulfate. This confirms the work of MacLeod et al. (1961a) that sulfite oxidase is absent in lung tissue.

Whole-body autoradiography of young male M.R.C. hooded rats following intraperitoneal injection of ^{35}S-sulfide and ^{35}S-sulfate, and sacrifice of animals at time intervals ranging from 3 minutes to 6 hours after injection, showed the label widely distributed and accumulating in tissues, including the gastrointestinal tract and cartilage. The uptake into bones indicated that oxidation to sulfate occurred prior to incorporation into mucopolysaccharides. In addition to these tissues and lung, radioactive label also accumulated in brain tissue and persisted there up to 20 minutes after sulfide injection (Curtis et al., 1972).

Further attempts to identify the locale of sulfide oxidation were made by Bartholomew et al. (1980), using ^{35}S-sulfide and isolated, living, perfused rat

livers, lungs, and kidneys. These experiments confirmed the plasma binding of sulfide (up to 90 percent bound) and the lack of sulfate formation in the lung. Release from carrier proteins in plasma and volatilization of sulfide to H_2S occurred, and 32 percent of the administered dose was lost from the blood through the lung. Sulfide remaining in the blood was oxidized slowly, possibly within red cells.

The same experiments with kidney confirmed the findings of Curtis et al. (1972) that sulfate was the major radioactive component in renal vein blood and urine, and that the kidney can oxidize sulfide. Bartholomew et al. (1980) found a mechanism for rapid oxidation of sulfide in liver mitochondria, which worked rapidly but only at low sulfide concentrations that did not inhibit cytochrome oxidase activity. Studies with isolated rat liver perfused with heparinized homologous blood to which a) $Na_2\ ^{35}S$ in phosphate buffer, and b) $Na_2\ ^{35}S$ and unlabeled thiosulfate in buffer, were added, showed significant metabolism of the sulfide to sulfate. After perfusion for 15 minutes in experiment (a) above, 70 percent of the radioactively-labeled sulfur was associated with sulfate, and the percentage increased to 82 percent after 2 hours perfusion. In experiment (b) above, 54 percent of the radioactive sulfur was found in thiosulfate after 15 minutes perfusion, with 22 percent ^{35}S in sulfate. After 30 minutes, the amount of label present in thiosulfate had decreased to about 30 percent, while that in sulfate had increased to about 46 percent. At the end of 2 hours perfusion time, only 13 percent of the label remained in the unreacted sulfide, and no radioactivity could be detected in thiosulfate. The work of these researchers confirmed the earlier work by MacLeod et al. (1961a,b) and Koj et al. (1967), which found thiosulfate to be a major oxidation product of sulfide and that thiosulfate was oxidized to sulfate in mitochondria. They proposed that glutathione mediated thiosulfate oxidation according to the following equations:

(1) $(S \cdot SO_3)^{-2} + 2GSH \longrightarrow HS^- + HSO_4^- + GSSG$ (oxidized glutathione)

(2) $SO_3^{-2} + \frac{1}{2}O_2 \longrightarrow SO_4^{-2}$

(3) $2HS^- + 2O_2 \longrightarrow (S \cdot SO_3)^{-2} + H_2O$

MacLeod et al. (1961 a,b) suggested that sulfite oxidase converted the sulfite intermediate to sulfate.

Weisiger and Jakoby (1979) have identified an enzyme, thiol-S-methyltransferase, which catalyzes the methylation of H_2S to methanethiol (CH_3SH), then dimethylsulfide (CH_3CH_3S). The authors regarded this methylation as a means of detoxification since both products are less toxic than H_2S. The enzyme is found primarily in gut mucosa and liver, and may thus serve to detoxify H_2S absorbed from that produced by anaerobic bacteria in the intestinal tract. The role of this enzyme in the detoxification of inhaled hydrogen sulfide has not been determined.

Reaction of H_2S with metallic-ion-containing protein is considered its major mechanism of toxicity (Smith and Gosselin, 1979). Chance and Schoener (1966) had found sulfide to be a stable inhibitor of mitochondrial heme-containing cytochrome enzymes which are involved in oxidative metabolism. Cytochrome aa_3 (cytochrome c oxidase, cytochrome oxidase) is the last enzyme in this complex of the cytochrome chain which transfers electrons to oxygen as the final electron acceptor, combining them with hydrogen ions to form water. In the presence of hydrogen sulfide, transfer of electrons to oxygen cannot occur, all electron transport down the chain is stopped, and oxidative metabolism, which is the primary energy source for mammalian cells, stops. Work by Wever et al. (1975), Nicholls (1975), Nicholls et al. (1976), Smith et al. (1977), and Smith and Gosselin (1979) showed that H_2S causes chemical reduction of one of the hemes of this enzyme, preventing electron transfer to oxygen. Chance and Schoener (1966) found that hydrogen sulfide inhibits cytochrome oxidase slightly more powerfully than hydrogen cyanide does, but the mechanism of action appears to be similar. Smith et al. (1977) also conducted *in vitro* experiments using sub-mitochondrial particles prepared from beef heart. They confirmed that sulfide is a more potent inhibitor of cytochrome oxidase than is cyanide. Nicholls (1975) showed similar results and determined the k_i for H_2S to be ~0.02 μM.

Inhibition of cytochrome oxidase through *in vivo* and *in vitro* experiments, and recovery from inhibition was shown by Torrans and Clemens (1982) in channel catfish (*Ictalurus punctatus*), in addition to measurement of some physiologic parameters (See Chapter 8, Section 8.1, Animal Effects). Both fathead minnows (*Pimephales promelas*) and channel catfish were exposed to 1.0 mg/liter H_2S (20 mg/liter total sulfide) at 20°C, water pH 8.0. Individual fish were removed from the sulfide solution when ventilation ceased (13-23 minutes for the channel catfish and 9-15 minutes for the fathead minnows) and tissues were removed for

homogenization and assay of enzyme activity. Cytochrome oxidase activities in the fathead minnows ranged from control levels in testes to 55 percent inhibition in kidney. In the channel catfish, the brain enzyme was inhibited 28 percent and heart enzyme 66 percent. Hydrogen sulfide (unionized) affected the catfish brain and gill cytochrome oxidase more than dissolved sulfide ion. When fish were exposed to 0.1 mg/liter H_2S at 10°C, brain enzyme was not affected, even at 30 minutes exposure, but gill enzyme was inhibited 15 percent after 5 minutes and 39 percent after 30 minutes exposure. At 0.3 mg/liter H_2S, brain enzyme activity was reduced by 25 percent, and at 0.5 mg/liter brain enzyme activity was inhibited 56 percent, while gill enzyme activity was reduced by 48 percent after 5 minutes exposure. This last was the maximum effect at that concentration and coincided with ventilatory arrest. Temperature had great effect on enzyme activity of fish exposed *in vivo*. Channel catfish exposed at 20°C to 0.1 mg/liter H_2S showed enzyme inhibition similar to those exposed to 0.5 mg/liter at 10°C. Thus, after 10 minutes exposure to 0.1 mg/liter H_2S for 10 minutes, brain cytochrome oxidase activity was 58 percent reduced, while gill enzyme was 41 percent decreased; after 20 minutes brain enzyme was 40 percent reduced, while gill enzyme was reduced 33 percent; after 30 minutes, brain enzyme was 40 percent and gill 26 percent reduced. Blood lactate levels increased as cytochrome oxidase levels decreased, indicating high levels of anaerobic metabolism, and the fish became rapidly fatigued. High levels of methemoglobin induced by pre-exposing fish to nitrite sulutions reduced the degree of cytochrome oxidase inhibition produced upon exposure to H_2S.

Torrans and Clemens (1982) also measured *in vitro* cytochrome oxidase inhibition by sulfide. Even very low concentrations inhibited the enzyme in tissue homogenates. Catfish brain-homogenate cytochrome oxidase activity was decreased 18 percent at 10^{-7}M H_2S, 64 percent at 10^{-6}M H_2S, and 100 percent at 10^{-4}M H_2S. Effects were similar for fathead minnow brain-homogenate. The pH of the solution influenced dissociation of H_2S and consequently its toxicity. At pH 5, and 10^{-6}M, 98 percent of the H_2S is unionized, and greatest inhibition (65.4 percent) occurred. As the pH of 7.04 was approached, inhibition decreased, more sulfide ion formed, and at pH 7.5 only 14 percent H_2S remained unionized, and enzyme inhibition decreased to 45.7 percent. The reaction was reversible, as was also shown *in vivo*, and showed competitive kinetics.

Since the effect of H_2S poisoning is to deprive the cellular cytochrome chain of oxygen, those cells having the highest oxygen requirement are most

rapidly and severely affected. Nerve tissue and cardiac tissue have large oxygen demands and show the first effects of hydrogen sulfide toxicity.

Besides cytochrome oxidase, other metallo-proteins also react with H_2S. When these are enzymes, perturbations of other pathways may occur, although this effect would be nearly overshadowed by the cessation of oxidative metabolism. Interactions of H_2S with horseradish peroxidase (Wieland and Sutter, 1928), potato polyphenol oxidase (Keilin, 1928), and catalase (Stern, 1932) produced inhibition of these enzymes, but the importance of these reactions to detoxification has not been further explored. Tenhunen et al. (1983) assayed *in vitro* enzyme activity for heme synthetase, and δ-amino-levulinic acid synthetase (AmLev synthetase) from human venous blood. These enzymes are part of the pathway in the synthesis of protoporphyrin, which is a precursor of heme. In 17 workers exposed to hydrogen sulfide and methylmercaptan, these enzymes showed decreased activity when assayed. Erythrocyte and protoporphyrin concentration in seven of these cases were below the control range. In the *in vitro* experiments, both hydrogen sulfide and sulfide anion inhibited heme synthetase and AmLev synthetase. These results may be of importance for their indication of a possible additional pathologic mechanism for H_2S poisoning, as well as a means of assessing worker exposure and/or health. However, it must be noted that the *in vitro* concentrations used to produce inhibition were considerably higher (3.4 to 10 mmol/liter) than the concentrations that workers exposed to low levels would experience.

Hydrogen sulfide can act as a reducing agent for disulfide bridges in proteins. Such change in protein structure has been proposed as an explanation for H_2S inhibition of succinic dehydrogenase. Whether inhibition of this enzyme has a role in the toxicity of H_2S has not been elucidated.

Reaction with methemoglobin constitutes a pathway for detoxification, resulting in the formation of sulfmethemoglobin. Smith et al. (1977) using submitochondrial particles from beef heart *in vitro*, showed that methemoglobin relieved the inhibition of cytochrome oxidase by H_2S by re-initiating the oxidation of ferricytochrome c. Smith and Gosselin (1966) showed methemoglobin formation in mice. Smith and Gosselin (1966), following up the work done by Scheler and Kabisch (1963) with rabbits, dogs and armadillos, pretreated mice with sodium nitrite before exposing them to inhaled H_2S and injected sodium sulfide. Nitrite causes the formation of methemoglobin. Smith and Gosselin (1966) also preinjected mice intraperitoneally with human methemoglobin prior

to injection of sodium sulfide. Both injected nitrite and methemoglobin protected the mice from death from subsequent injections of sodium sulfide. It should be noted that such prophylactic treatment of humans with potential of exposure to hydrogen sulfide is of little practical value.

Antidotal effects of nitrite were shown in mice and rabbits by Gunter (1953) and in mice by Scheler and Kabisch (1963). The course of poisoning was reversed in mice after they showed severe signs of intoxication and the rabbits and mice survived even six times the usual lethal dose of ammonium sulfide. Smith et al. (1976) showed that the number of mice surviving a lethal dose of injected sodium sulfide increased significantly when it was followed by an injection of sodium nitrite within two minutes. Smith and Abbanat (1966) had shown earlier that glutathione could have a protective effect against H_2S poisoning in mice, probably by tying up HS^- through the disulfide linkage of oxidized glutathione (GSSG).

A single case of severe H_2S intoxication in humans has been treated with nitrite. It is described in detail in Section 8.2, Human Health Effects. There is some doubt that a treatment which brings about hypoxemia is of practical value for poisoning victims whose ability to use oxygen is already compromised. More effective treatment shown in rats, used alone or as an adjunct to methemoglobinemia induction by nitrite injection, is hyperbaric oxygen therapy with one to three ATA (atmospheric absolute) oxygen (Bitterman et al., 1986).

Beck et al. (1982, 1983) demonstrated an anesthetic-like effect of both H_2S and HCN at high concentrations (5,300 to 987,000 ppm H_2S) on isolated nerve preparations from the frog Rana pipiens. Changes in membrane function led them to suggest not only an inhibition of cytochrome oxidase, but also a conformational H_2S or HS^- induced change in membrane proteins, which they suggest might account for some of the evidence of permanent nerve damage seen in some recovered victims of H_2S poisoning. The exposure concentrations used far exceed those from which victims usually recover, however. Such possible change in membrane protein conformation has not been further investigated. Other explanations for permanent nerve damage are equally or more plausible. Examples of phenomena which have been explored are damage done directly to nerve cells by anoxia (Yap and Spector, 1965; Yanagihara, 1976; Elovaara et al., 1978; Savolainen et al., 1980; Metter and Yanagihara, 1979) and damage done by ischemia following anoxia.

7.3 EXCRETION

While H_2S usually enters via the lung, this organ can also serve in an excretory capacity. Evans (1967), working with cats, showed that some of the sulfide from injected sodium sulfide was exhaled. The percentage eliminated depended on the site of injection, but the variation in injection site was related to a variation in the length of time that sulfide was free in the blood. Zero to 37 percent of H_2S and NaHS injected into the abdominal aorta was eliminated through the lung, while 26.5 percent was exhaled when sulfide was injected into the external jugular vein. The external jugular joins the vena cava, and blood flowing through it enters the pulmonary circulation almost immediately. There is little time for interaction of sulfide with blood components or with organs whose tissues can metabolize H_2S, before it is exchanged in the lung. The abdominal aorta, in contrast, is near the beginning of the systemic circulation. Sulfide injected here has to make a full circuit of the vascular system before reaching the lung. Curtis et al. (1972) demonstrated clearly that sulfide binds to plasma proteins, primarily the albumin fraction, until it is oxidized to sulfate and excreted in the urine. The bound sulfide would not be exhaled.

Perfusion experiments indicate that various organs act as sinks for sulfide. The liver is the most significant sulfide sink, with metabolism there producing a number of sulfur-containing intermediates. Sulfate is the end-product of oxidation and is excreted in the urine (Curtis et al., 1972). A small amount of sulfide is oxidized to sulfate by sulfite oxidase, and is eliminated in the bile, appearing in the feces for excretion. The sulfate that is not excreted is widely distributed in tissues and incorporated into tissue proteins, as shown through autoradiography and other radioactive tracer methodology by Curtis et al. (1972).

The principal fate of injected sulfide is oxidation to sulfate and excretion in urine (Curtis et al., 1972). Sodium ^{35}S-sulfide administered intravenously to rats resulted in 45 percent of the radioactively-labeled sulfur appearing in the urine as sulfate within the first six hours after injection. Only small amounts (4.7 to 5.0 percent) appeared in the bile, indicating that the liver is not a major site of excretion.

7.4 REFERENCES

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8. TOXICITY

8.1 ANIMAL EFFECTS

Hydrogen sulfide poisoning attracted the interest of a number of excellent experimentalists during the nineteenth century (see review by Mitchell and Davenport, 1924). The characteristic respiratory excitation caused both by inhalation of the gas and by injections of hydrogen sulfide and sodium sulfide were described by the mid-1800's. Also known was the high lethality of hydrogen sulfide, its ability to cause respiratory arrest, its irritant effect, and the efficacy of removing victims from the contaminated environment and reviving them with artificial ventilation (Lehmann, 1892).

An early hypothesis which postulated that H_2S was a blood poison similar to carbon monoxide sidetracked advances in determining the toxicologic mechanism. Hoppe-Seyler (1863), Eulenberg (1865), and others concentrated on the interaction of hydrogen sulfide with hemoglobin, despite the lack of experimental proof in poisoned animals that the reaction of sulfide with hemoglobin was significant. The emphasis for this line of research undoubtedly came from the post-mortem finding in human poisoning victims of massive sulfur compound discoloration of tissues and blood, which occurs when enzymes are no longer capable of metabolizing the sulfide. Two significant toxicologic endpoints have been identified for hydrogen sulfide. It irritates mucous membranes, causing damage to eyes and trauma to lungs that can be lethal. Hydrogen sulfide is an acid in solution, with 2 pKa values, one at 7.04 and the other at 11.96. Its acidic nature, plus its interaction with membrane proteins, may account for its irritant effect. Its most significant, potentially lethal effect, is that it acts as a respiratory poison, halting oxidative metabolism. Tissues of systems with high oxygen demands, such as the nervous and cardiovascular systems, suffer the most immediate and the most damaging effect of the poison.

8.1.1 Effects at High Concentrations

Haggard et al. (1922) demonstrated dramatically the lethal effect on dogs exposed to hydrogen sulfide at a concentration of 0.1 percent by volume, or 1000 ppm. Death ensued within 15 to 20 minutes of exposure time. Respiration was stimulated immediately as the dogs breathed the gas, leading to strong hyperpnea, followed by cessation of breathing, which resulted in death.

If the dosage of H_2S was increased to 0.3 percent by volume (3000 ppm) of inspired air, respiration was arrested after a few gasps.

Similar effects were demonstrated when dogs were injected intravenously with sodium sulfide, with the exception that no pulmonary edema was seen. The dogs began immediate hyperpneic breathing when injected with doses of 2 to 4 mg H_2S/kg. Hyperpnea was followed by variable periods of apnea, which was relieved by artificial ventilation. Haggard (1925) indicated that vagotomy eliminated the stimulatory effects of H_2S on respiration, but a more convincing case was made by Heymans et al. (1931, 1932) for a role of the carotid sinus chemoreceptors (carotid bodies) in initiating an increase in respiratory rate and depth upon interaction with hydrogen sulfide at sublethal levels. Heymans et al. (1931, 1932) showed that injecting a small amount of sodium sulfide into the common carotid artery of dogs elicited an immediate and forceful increase in ventilation (hyperpnea). After denervation of the sinus or transection of the sinus nerve, larger doses of sulfide had no immediate effect on respiration, and the late effect was respiratory depression. Injection of sodium sulfide into the internal carotid, distal to the chemoreceptors, or into the vertebral arteries, had the same effect as on denervated animals. Sulfide injected here would be diluted by the general circulation, and also metabolized, before it reached the chemoreceptors.

Cross-perfusion techniques, in which isolated carotid sinuses of a recipient dog received the entire blood supply from a donor dog, were used by Heymans and co-workers to confirm these results. Sodium sulfide injected into the recipient dog's general circulation had no respiratory stimulatory effect; the carotid chemoreceptors were not part of its circulation; when sodium sulfide was injected systematically into the donor dog, whose blood perfused the recipient's chemoreceptors, the response was elicited. A similar, although secondary, response was shown with the aortic chemoreceptors by Heymans and Neil (1958).

Other experimenters, including Owen and Gesell (1931), Winder and Winder (1933), and Evans (1967), supported the work of Heymans and Neil (1958). Evans confirmed that doses in the range of 20 μmol/kg sodium sulfide injected intravenously into cats caused an immediate hyperpnea, often followed by permanent respiratory arrest. If the carotid sinus region was anesthetized, the hyperpnea did not occur, but in a single trial, when the sulfide was injected into the ascending aorta where it could interact with the aortic chemoreceptors, hyperpnea still occurred.

Ever since Heymans et al. (1932) elucidated the controlling role of the carotid bodies in the reflex governing ventilation, researchers have puzzled over the seeming paradox presented by the effect of hydrogen sulfide on the nervous system. While the dominant effect is a depression of function, manifested as a paralysis of ventilation and loss of the sense of smell, the neural receptors of the carotid and aortic bodies appear to be stimulated. The immediate effect of sublethal doses of H_2S is on these receptors, resulting in intense stimulation of the ventilatory reflex. Both rate and depth of ventilation increase to the point of hyperpnea. As exposure to H_2S continues, respiration ceases because of paralysis of the central respiratory centers. The effect on carotid and aortic bodies seems inconsistent with the depressant effect on the central nervous system, as well as that demonstrated with H_2S on isolated nerve preparations. Early researchers of this phenomenon (Haggard, Heymans, Evans) did not offer an explanation for this seeming contradiction, yet clearly ascertained that it existed.

It is possible to resolve this paradox if the normal function of the carotid and aortic bodies is examined together with the cellular effect of hydrogen sulfide.

The reflexes associated with the chemosensors of the carotid and aortic bodies function physiologically to maintain a ventilation rate and depth that is adequate for supplying tissue cells with oxygen. The chemosensors' primary sensitivity is to the partial pressure of oxygen (pO_2), or oxygen tension, in blood flowing through the carotid sinuses and the aortic arch. Under normal conditions, no oxygen is removed from the blood before it reaches these vessels, so that pO_2 is between 100 and 104 mm Hg, at which hemoglobin is saturated with oxygen. Oxygen tension must decrease considerably for the reflexive increase in ventilation to be activated. The carotid and aortic chemosensors do not respond with rapid impulse firing until the pO_2 falls into

the 60 to 30 mm Hg range (Biscoe, 1971). Such a decrease normally occurs only with hypotension, if the systolic arterial blood pressure falls below 80 mm Hg. When the oxygen tension falls together with blood pressure, the chemosensors, in concert with the baro- or pressure sensors in the same blood vessels, initiate reflexes to increase rate and depth of ventilation and increases in blood pressure, which can lead to restoration of normal pO_2 under normal circumstances.

This same response is seen in sublethal H_2S poisoning. Yet this poison inhibits neural function. It most rapidly affects the intracellular mitochondrial enzyme cytochrome oxidase, interfering with the transfer of electrons and hydrogen ions to oxygen, thus blocking oxidative metabolism. Cells most dependent on oxidative metabolism, and/or those having a high oxygen demand, such as those of the nervous system or the heart, would be most rapidly and severely affected. In the case of the carotid and aortic chemoreceptors, halting of oxidative metabolism has the same effect as a decrease in oxygen supply. As oxidative metabolism in these highly sensitive nerve endings stops, they respond with rapid-fire impulses to the respiratory centers, initiating the reflexive increase in rate and depth of ventilation, just as when pO_2 falls below 60 mm Hg. Reflexive hyperpnea is therefore a logical consequence of the inhibition by H_2S of cytochrome oxidase in the chemosensors of the carotid and aortic bodies (Ammann, in press).

It is also observed that H_2S inhibits the respiratory centers in the central nervous system, producing apnea at high concentrations or with prolonged exposure to the gas.

The physiologic and biochemical action of sodium sulfide and hydrogen sulfide on fish was determined by Torrans and Clemens (1982). They exposed channel catfish (Ictalurus punctatus) which were implanted with electrodes in the opercular muscle and near the heart so that ventilation and heart rates could be monitored. Acute exposure (0.5 mg/liter hydrogen sulfide for one minute at 20°C) resulted in an initial stimulation of heart rate and amplitude of ventilatory movement. Heart rate increased from a resting rate of 88 to 128 beats/minute (b.p.m.), while ventilation rate decreased from 140 to 128 cycles per minute, but with greater amplitude of opercular movement. After 5 minutes exposure the heart rate decreased to 60 b.p.m.; ventilation rate decreased to 88 c.p.m., and both became shallow and irregular. After 6 minutes and 40 seconds exposure the opercular muscle went into a state of tetany and

ventilation ceased. When the fish were returned to fresh water after 8 minutes exposure, the opercular muscle showed occasional spasms, but ventilation was not restored, although the heart continued to beat with a steadily decreasing rate for one hour. The effect of hydrogen sulfide *in vivo* and *in vitro* on cytochrome oxidase and on blood lactate levels was determined and is discussed in detail in Chapter 7, Section 7.2, Metabolism and Pharmacokinetics. Fish exposed so that brain cytochrome oxidase was inhibited 50 percent recovered full enzyme activity 6 hours after they were returned to fresh water, showing that inhibition is reversible and non-cumulative.

8.1.2 Effects at Intermediate Concentrations

Experiments on dogs, performed by Haggard et al. (1922), showed striking differences in toxic response depending on the dose of hydrogen sulfide administered. At a level considered to be the minimal lethal concentration (0.05 percent by volume in air, or 500 ppm), the respiratory rate of the animal showed a slight yet progressive decrease. Depth of respiration was likewise progressively depressed. Death resulted from pulmonary edema after many hours (unspecified) of exposure to the gas.

Hays et al. (1972) exposed mice and goats to H_2S in exposure chambers, and dairy cows in head-only chambers. Each goat or cow served as its own control, as did groups of mice equal in number to the test mice. Body weight, food and water intake were measured in all animals. Rectal temperature was measured in goats and mice, heart rate in goats and cows, and milk production in cows. Plasma cortisol concentration in goats, and carbonic anhydrase activity and phenobarbital sleeping time in mice were also recorded. Goats were individually exposed, but data were pooled in experimental or control groups of 3 to 5 animals. The only statistically significant change in cows at 20 to 50 ppm was a decrease in milk production. They showed discomfort and alteration in normal body function. Goats showed a 50 percent mean increase in plasma cortisol levels at 100 ppm H_2S. At 10 and 20 ppm H_2S for 48 hours exposure, mice showed no changes except depressed food and water intake and decreased body weight. The LC_{50} for mice was 100 ppm for 7.5 hour, 50 ppm for 15-hour, and 30 ppm for 18.5-hour exposures. Table 8-1 lists lethal concentrations reported for some mammals by various authors.

TABLE 8-1. REPORTED MAMMAL LETHALITIES

Animal Species	Type of Effect	Chemical Species	Concentrations	Reference
Mice	LD_{67}	Na_2S	0.55mM/kg	Smith and Gosselin (1966)
Mice (male)	LD_{50}	Na_2S	0.25mM/kg	Smith et al. (1976)
Mice	LD_{50}	Na_2S	0.32mM/kg	Smith and Gosselin (1979)
Mice	LD_{50}	HS^-	0.50mM/kg	Elovaara et al. (1978)
Mice	LC_{50}	H_2S	100 ppm for 7.5 hr 50 ppm for 15 hr 30 ppm for 18.5 hr	Hays et al. (1972)
Rats (Charles River)	LD_{75}; 5 min	Na_2S	55 mg/kg	Bitterman et al. (1986)
Rats (Sprague-Dawley)	LC_{50}; 24 hr	H_2S	444 ppm	Tansy et al. (1981)
Cats	LD_{50}	H_2S	0.025mM/kg	Evans (1967)

8.1.3 Effects at Lower Concentrations

Ninety-day vapor inhalation toxicity studies were conducted for the Chemical Industry Institute of Toxicology (Toxigenics, 1983a, b, c) on Sprague-Dawley rats, Fischer-344 rats, and $B_6C_3F_1$ mice. Three groups of animals at 10.1, 30.5 and 80 ppm, and controls were studied. No evidence of tissue pathology was found other than inflammation of the nasal mucosa in the anterior segments of the nose. There was a significant decrease in body weight gain in all animals treated with 80 ppm H_2S, and a depression in brain weight versus that of controls in the Fischer 344 rats treated at high exposure levels of 80 ppm.

This highly detailed study included neurologic function tests assessing posture, gait, and tone of facial muscles, and examining pupillary, palpebral, extensor thrust and crossed-extensor thrust reflexes, before and after exposure. Eyes were examined with both monocular ophthalmoscope and slit-lamp bimicroscope at the end of the exposure period. Extensive clinical pathologies included blood volume, appearance, occult blood, specific gravity, protein, pH, ketone

and glucose. Hematologic parameters and serum chemistry parameters were determined. Detailed necropsy examination was made, individual major organs were excised, and tissues were collected and examined microscopically. Included were brain (cerebellum and two levels of cerebrum, medulla, optic nerve), spinal cord (cervical, thoracic and lumbar--two sections each), peripheral nerves (sciatic and anterior tibial, with remaining sciatic nerve removed and stored in buffered formalin), eyes, pituitary, thyroid, parathyroid, salivary glands (submaxillary), heart, lungs (four levels), spleen, liver, pancreas, adrenals, lymph nodes (mesenteric and mandibular), kidneys, bladder (inflated with formalin), lacrimal glands, ovaries, uterus, oviducts, vagina, cervix, stomach, small intestine (duodenum, jejunum, ileum), large intestine (large and small colon and caecum), skeletal muscle (thigh), skin, mammary glands (males and females), bone (femur), bone marrow (smear and section), aorta, ear canal with zymbal gland, nasal turbinates (four levels), trachea, testes, epididymis, esophagus, thymus, prostate, seminal vesicle, and any gross lesion(s).

In addition, a special neurological study was performed on the two strains of rats:

> Five male and five female rats from each exposure concentration and the control group were used exclusively for the following study. Rats were perfused via the left ventricle with 4 percent phosphate buffered glutaraldehyde solution following anesthetizing with sodium pentobarbital solution containing approximately 200 units of heparin. The intact perfused animal was refrigerated at approximately 4°C overnight, after which the right and left sciatic nerve and their branches were dissected together with specimens of the cervical and lumbar spinal cord and placed in 4 percent glutaraldehyde. The left sural nerve and the large muscle branch of the left tibial nerve were osmicated and placed in cedarwood oil for approximately two weeks. Nerve fibers from the cedarwood oil treated specimens were teased to separate the individual fibers, then mounted on glass slides. The teased nerve fibers were coverslipped and retained as permanent specimens. A minimum of 50 teased fibers per rat (approximately 25 per nerve) were prepared. Glutaraldehyde fixed specimens of the right sural nerve, the muscular branch of the right tibial nerve, and specimens of the spinal cord from the cervical and lumbar regions were osmicated, dehydrated, and embedded in Epon. Thick sections (longitudinal and cross) of the nerves and cross sections of the spinal cord, were prepared from the Epon specimens and stained with toluidine blue. Other tissues were stored in 10 percent neutral buffered formalin. Specimens were examined by routine light microscopy for evidence of pathologic change. The control and highest exposure groups were examined initially. If changes were detected, lower exposure groups were to be examined.

No lesions or significant changes in any of the parameters examined, aside from body weight and brain weight changes, could be statistically attributed to exposure of the animals to H_2S.

The 1982 Lodgepole gas well blowout exposed farm animals to levels of 10 to 15 ppm H_2S, as well as to other gaseous constituents of the well effluent. Members of the community described problems in cattle, pigs, horses, and household pets. They noted that the animals suffered runny noses and eyes, coughing, and decreased food intake. Most cattle in the exposed area were affected, young animals showing more severe signs of irritation of mucous membranes than old. Residents also testified that some animals suffered from diarrhea, red stools, red urine and decreased weight gain. A local veterinarian and members of five families described an almost total disappearance of small wild animals and birds, which did not reappear for a long time after the blowout had been controlled (Lodgepole Inquiry Board Report, 1984; Herbert, 1985).

The Alberta Environmental Centre staff measured some significant changes in the activity of certain enzymes in the blood of cattle exposed to emissions from the Lodgepole blowout. The enzymes superoxide dismutase, glutathione peroxidase, glucose-6-phosphate-dehydrogenase, acetylcholine esterase, and aspartase aminotransferase were selected as being involved in the detoxification of H_2S or otherwise affected by it (Beck, 1985). The changes appeared to be transient and reversible, and their importance or their possible relationship to clinical disease in the exposed animals is not known (Prior and Coppock, 1986; Harris, 1986).

Similar findings of signs of eye and respiratory irritation in cattle and horses was reported by a veterinarian following a well blowout in 1984 (Drummond 6-30 Sour Gas Well Blowout). Alberta Environment Centre and Alberta Agriculture staff followed up livestock on sixteen farms, beginning the day following the blowout and continuing over the next three months. Owners of livestock were contacted a year later to determine if any unusual health problems had occurred. Immediate complaints following the blowout generally consisted of irritation of ocular and respiratory membranes, respiratory disease (pneumonia), reduced exercise tolerance, and reproductive failure. The investigation team concluded that eye and respiratory irritation could be attributed to exposure to the wellhead emissions and may have made animals more susceptible to the

effects of infective keratoid conjunctivitis (pink eye) and infective respiratory disease (pneumonia). Decreased exercise tolerance of horses, and loss of weight, condition and appetite may have been caused by exposure to gases. No consistent patterns of animal disease could be identified. Concentrations ranged from 0.014 mg/m^3 to 4.90 mg/m^3 (0.01 to 3.50 ppm), with a mean concentration over the 4 days of the episode of 0.51 mg/m^3 ± 0.80 (0.36 ppm ± 0.57) (Alberta Agriculture, Alberta Environment Centre, 1986).

8.1.4 Toxic Effects on Various Animal Tissues

While there is information on a variety of systems in animals, there is no complete picture of any specific organ toxicity or toxicity to specific organ systems. A number of studies have addressed changes in enzyme activity and concentrations (Elovaara et al., 1978; Savolainen et al., 1980; Cohen and Hochstein, 1965; Husain and Zaidi, 1977; Husain, 1976).

8.1.4.1 Brain. Elovaara et al. (1978) demonstrated a marked decrease in mouse brain protein synthesis after 2 hours exposure to 100 ppm H_2S, as shown by a decrease in ^{14}C-leucine incorporation. They found in subsequent experiments (Savolainen et al., 1980) that this decrease in protein synthesis correlated with an increasing inhibition of cerebral cytochrome oxidase with repeated exposures of 2 hours at 4-day intervals to 100 ppm hydrogen sulfide. Nicholls (1975) showed that hydrogen sulfide forms a heme-sulfide complex which is very slow to dissociate (K_i ~0.02 μm for H_2S). Repeated exposure to the gas would cause increasing numbers of complexes to form, resulting in less and less oxidative metabolism in the affected cells. The limiting factor in recovery would be the rate of synthesis of new heme. The half-life of heme exceeds 24 hours (Shanley et al., 1977). While these studies indicate a cumulative effect on the brain from hydrogen sulfide poisoning, similar damage is seen as a result of anoxic episodes (Yanagihara, 1976; Yap and Spector, 1965). In anoxia there is also a decrease in protein synthesis as well as RNA synthesis, and a decrease in formation of polyribosomal complexes (Yanagihara, 1976).

Anatomic changes in brain tissues with exposure to H_2S were investigated by Lund and Wieland (1966) in three rhesus monkeys. One was killed by inhalation of a high dose (500 ppm) of H_2S. No pathologic changes were seen in fixed and stained tissue sections of brain, kidneys, adrenal glands, or heart. The liver of this animal was severely hyperemic, with dilation of its blood vessels.

The second monkey was exposed for 35 minutes until breathing ceased; it was revived and exposed again until it lost consciousness, and then revived. Five days after exposure, it was sacrificed and its tissues examined. Histologic examination of the brain showed spotty regions of altered cells and a noticeable vascularization in the region of the basal ganglia, in the upper parts of the putamen, and on the caudate nucleus. The lesions characteristically had newly formed capillaries and increased glial formation. The cortex of the occipital lobe was altered, with lamellar separations between the lower layers of cortex. The smaller blood vessels of the cortex were hyperemic. Necrosis of the parenchymal cells of the cortex was evident. No pathologic lesions were seen in tissues other than the brain. The liver was, however, severely hyperemic.

The third rhesus monkey was exposed as was the second, but exposure was interrupted after 22 minutes. Spontaneous respiration never ceased, but the monkey was somnolent, ataxic, anorexic, relatively immobile, and uncoordinated in those movements that he made. The animal improved only slightly, and was sacrificed after ten days.

Examination of the brain again showed damage in the basal ganglia, an increase in glia, and spotty lesions of the cortex in the parietal and occipital lobes. There was a decrease in the Purkinje cells in the cerebellum. No pathologic lesions of the kidneys, adrenals, heart, or liver were seen.

Dahme and co-workers (1983) examined the brains of eight cattle whose survival time after H_2S poisoning ranged from 18 hours to 10 days. Histological examination of the brain disclosed spotty regions of neuronal necrosis with vascular proliferation and gliosis in the basal ganglia. Laminar necrosis of the cerebral cortex was also noted, particularly in the occipital cortex. Up to 60 hours after intoxication, bilaterally symmetrical lesions were seen in the dorsal neocortex and, to a somewhat lesser degree, in the cornu Ammonis of the hippocampus, the lateral geniculate nucleus, the globus pallidus, the caudate nucleus, and the cerebellar Purkinge cell layer. These lesions were characterized by eosinophillic neuronal necrosis and astrocytic edema, accompanied by low grade edema of the white matter. At later time points, up to 10 days post-exposure, the lesions had progressed to laminar necrosis with resorption of necrotic tissue by macrophages.

The lesions described in these experiments are those which are seen in systemic hypoxia and in intoxications which impair tissue utilization of

oxygen, such as carbon monoxide poisoning. It is doubtful that hydrogen sulfide poisoning results in toxicity through mechanisms other than interference with oxidative metabolism.

8.1.4.2 Lung. That other enzymes besides cytochrome oxidase may be directly inhibited by H_2S is supported by the work of Husain (1976) and Husain and Zaidi (1977). This work investigated various enzyme activities in lung homogenates from rats. The homogenates were exposed by bubbling H_2S gas through them, and enzyme activities were measured by accepted techniques. At 18 ppm, H_2S inhibited acid phosphatase, alkaline phosphatase, glutamic-pyruvic transaminase, glutamic-oxaloacetic transaminase, and ATPase by 16.8, 11.0, 25.9, 15.9, and 13.3 percent, respectively. As H_2S concentration increased, the inhibition of these enzymes also increased. Fructose 1,6-diphosphate aldolase activity was unaffected by H_2S, while arginase activity was stimulated with increasing gas concentrations. The authors postulate that metallo-sulfate complexes are formed from the interaction with H_2S, and that H_2S also combines with the enzyme cofactor pyridoxal phosphate in the case of the transaminases. Such interactions with enzymes other than cytochrome oxidase could contribute to possible cumulative cellular damage from either long-term, low-level, or repeated exposure to hydrogen sulfide gas. However, direct evidence for the formation of such complexes is lacking.

8.1.4.3 Heart. Kosmider et al. (1967) exposed rabbits to 100 mg/m^3 (~71.4 ppm) for periods of one to five hours, until they lost consciousness, and others for 0.5-hr periods daily for 5 days. Electrocardiograms showed that the acutely poisoned animals' hearts showed disorders of repolarization. The subacutely poisoned animals exposed repeatedly to H_2S consistently showed arrhythmias in the form of ventricular extrasystoles and bigeminal rhythms. This group, like the acutely poisoned group of animals, displayed disorders of ventricular repolarization seen as flattened T-waves. When animals with H_2S-induced arrhythmias were treated with calcium-binding compounds, such as sodium citrate, normal rhythms were restored. Arrhythmias returned in several instances, and repeated doses of sodium citrate had to be used after several hours to restore physiologic rhythms.

Kosmider et al. (1967) followed these experiments with histochemical studies. Fragments from the apical region of the heart and from the heart vasculature were examined for activity of two enzymes. They found that ATP phosphohydrolase activity in blood vessels and the sarcolemma of the heart muscle cells was decreased in exposed animals, compared to that in controls.

$NADPH_2$ oxidoreductase activity in heart muscle cells and vascular endothelium was likewise reduced. It is not possible to distinguish whether these effects result directly from H_2S toxicity on the cells examined or whether they are secondary effects of hydrogen sulfide poisoning of the whole animal. The authors state that these effects are the result of H_2S action directly on the heart.

Changes in activity of these enzymes affected the active transport of sodium and potassium ions in the heart muscle cells and the walls of blood vessels. These changes lead to changes in concentrations of these ions across heart cell membranes, which in turn cause changes in electrical activity. These changes can account for the observed differences in rhythm and repolarization in the experimental animals. The significance of these observations is that changes in heart function may be a direct response to hydrogen sulfide by heart cells, rather than a secondary response elicited by the action of the nervous system on the heart. Since other enzyme activities were not measured, nor were in vitro enzyme assays done, it is unclear whether the decrease in activities is directly attributable to action of H_2S on the enzymes, or to interference with oxidative metabolism by the gas.

8.1.4.4 Other Tissues. Voigt and Müller (1955) exposed seven guinea pigs and seven rats to hydrogen sulfide in order to examine the formation and localization of sulfate complexes in the animals through histochemical techniques. They exposed the guinea pigs for 0.5, 1, 2, and 2.5 hours, and the rats to 1 minute, 1.5 hours and 10 hours. H_2S concentration measurements were not made, though they were sufficiently high to produce obvious symptoms of intoxication; in most cases they were low enough to allow sufficient survival time for the animal to distribute and metabolize the hydrogen sulfide. Most of the animals were subjected to poisoning by inhalation, although one rat (under anesthesia) had the skin dissected from its thigh, which was then immersed in warm saline through which H_2S was bubbled. This animal was killed after 35 minutes exposure. Another rat (also anesthetized) had H_2S instilled directly into its abdomen through a small incision, which caused death after ten minutes. Three guinea pigs and three rats not exposed to H_2S underwent the same histochemical preparation, and their tissues served as controls. A silver stain was used to localize sulfur (sulfate) complexes. Most animals were killed and fixed immediately following exposure, or died from the exposure and were fixed, with the exception of one guinea pig, which was removed from the gas chamber because

of respiratory spasm, and it was allowed to live until it died of edema of the lung 2 hours later. It was then fixed and stained.

Sulfate complexes were located in tissue preparations by the formation of darkly stained silver granules in the tissues. Examination under low magnification established the tissue localization, while high magnification localized cellular deposits. Degree of granule formation was related to exposure time. Those animals exposed for short time periods, even those exposed to concentrations sufficient to cause rapid death, showed none or few granules deposited in any tissue. Animals that were exposed for longer time periods (e.g., for 2 hours), presumably allowing tissue distribution and metabolism, exhibited high concentrations of granules in brain, liver, kidney, pancreas, and spleen.

Deposits of granules occurred both in nervous and glial cells of the brain, concentrating especially in nuclei and nucleoli of cells. In a few animals, silver granules were found in the nuclei of brain capillary cells and in the perivascular space, and especially along the basal membrane of the capillaries.

Liver distribution of silver granules in animals exposed for longer time periods occurred primarily in the cords of liver cells, whose cell nuclei and nucleoli were heavily stained. Silver staining in kidney was virtually limited to the cell-plasm of the epithelia of the medulla. Silver grains were also seen in the thin section of the loop of Henle, down to the turn of the loop but decreased in the ascending portion. Not all nephrons were equally stained. In one guinea pig exposed for 2 hours and one rat exposed for 1.5 hour, concentrations of silver grains were seen in the epithelia of the collecting ducts. The basal membrane of those nephrons exhibiting staining was heavily stained. The pancreas of long-exposed animals showed silver stain in the exocrine portion of the organ, especially in the alveolar spaces of the ducts, being more heavily concentrated in the periphery of the cells and localized in what are identified as zymogen granules, with other staining techniques. Islets of Langerhans showed no silver granules. The control animals showed no accumulation of silver granules in any of the tissues examined.

Of great significance is the single guinea pig which died of lung edema after a two-hour recovery time, post-exposure. Its tissues showed no accumulation of silver grains except for a few in the kidney tubules. This may be of particular importance in the interpretation of results, especially in determining whether persistent sulfate complexes result, which could be responsible

for long-term health effects from H_2S poisoning. The indication here is that these sulfate complexes are transient and are either metabolized or excreted relatively quickly after being formed.

The authors propose, but show no evidence for, the formation of sulfate complexes with trace heavy metals, especially iron. The localization of granules in nuclei, nucleoli, basal membranes and in what appear to be zymogen granules, suggest that binding to protein may be an equally plausible hypothesis, which could be supported by the relatively rapid turnover of the sulfate complexes.

Hydrogen sulfide may have an effect on the immune system, decreasing the ability of animals or humans to withstand infection. Rogers and Ferin (1981) exposed male Long-Evans rats in nose-only exposure chambers to 45 ppm H_2S for 2, 4 and 6 hours. Immediately following exposure, rats were anesthetized and challenged with a 30-minute staphylococcal (coagulase negative Staphylococcus epidermidis) aerosol through a nose-only exposure chamber. Rats were killed at 30 minutes (time 0), 3 hours, and 6 hours post-bacterial challenge, along with a control rat for each time period. Exsanguinated lumps were excised and homogenized (in a procedure that did not alter the viability of the bacteria) and the homogenates were plated and grown on a selective growth medium for staphylococci, and colonies were counted after incubation of plates for 48 hours. Rats exposed for 4 hours to H_2S had 6.5-fold greater percent colony forming units (CFU) than controls ($P < 0.01$), while the 6 hours H_2S-exposed group had a 52-fold greater percent CFU than controls ($P < 0.01$). Since there was no evidence of pulmonary edema to promote bacterial growth, and since bacteria are normally rapidly phagocytized by pulmonary macrophages, it can be concluded, as the authors conclude, that H_2S significantly impaired the antibacterial system of the rats by impairing pulmonary macrophages. Such impairment could contribute to the development of secondary pneumonias in humans and animals subsequent to sublethal H_2S exposure.

8.1.4.5 Similarities of H_2S Effects to Anoxia. While the lesions described in these experiments may be attributable specifically to hydrogen sulfide poisoning, the damage is also characteristically seen in carbon monoxide poisoning and in brain anoxia (Savolainen et al., 1980; Yap and Spector, 1965; Yanagihara, 1976). The cellular changes in number and kind, as well as the enzymatic changes that have been delineated in tissues of animals exposed to low levels of hydrogen sulfide, correlate very closely to those seen in animals recovered from anoxia episodes (Yap and Spector, 1965; Yanagihara, 1976; Elovaara et al.,

1978; Savolainen et al., 1980). While there exists some evidence that other enzymes play a role in cellular dysfunction, the predominant damage seen in all tissues is due to the inhibition of cytochrome oxidase. Those tissues with the highest oxygen demand, such as neural and cardiac tissues, sustain the most rapid, consequential, and lasting damage. Dahme et al. (1983) support these findings.

8.2 HUMAN HEALTH EFFECTS

8.2.1 Potentially Lethal Concentrations

Systemic poisoning at exposures of 500 to 2000 ppm primarily targets the nervous system, although other tissues with high oxygen demand, particularly the heart, are also affected. Usually acute intoxication occurs from a single, massive exposure of 2000 ppm or more, and unconsciousness occurs within a few seconds, without significant warning or pain. Unconsciousness, termed "knock-down" by workers, is almost immediately followed by respiratory paralysis, and after that by a short period of tonic convulsions (Yant, 1930). The heart continues to beat for several minutes. Death occurs unless the victim is removed from the contaminated area, and artificial ventilation is immediately initiated. Pettigrew (1976) reports that 26 persons died from exposure to hydrogen sulfide, at unspecified concentrations, between October 1, 1974 and April 28, 1976 in the high-sulfur oil fields of Wyoming and Texas. Victims exposed to less massive doses will recover spontaneously at times, provided they have been removed from contamination.

If the victim is not removed from the gaseous environment and given artificial ventilation, spontaneous recovery of ventilation may not occur and death may ensue. Even if ventilation does resume, asphyxia will eventually occur with continued exposure if the victim remains in the contaminated environment. Animal data indicate that this is due to inactivation of cellular respiration, specifically the reversible inhibition of cytochrome oxidase, as described previously. According to Haggard (1921), breathing is never spontaneously restored after respiratory paralysis occurs from H_2S exposure, and death from asphyxia will occur. If artificial ventilation is used, recovery may be immediate and complete. It should be noted that victims need to be removed from exposure immediately and their ventilation assisted. Rescuers must know that self-contained breathing apparatus are absolutely required if contaminated areas are to be entered. Many potential rescuers have succumbed,

together with victims of H_2S exposure who might have been saved, because they were unaware of the lethality and rapid, overwhelming action of this toxic gas (Kleinfeld et al., 1964; Adelson and Sunshine, 1966; Simson and Simpson, 1971; Smith and Gosselin, 1979). Occasionally there are some lingering effects, such as nystagmus and disturbances of equilibrium, suggesting ototoxic effects. Changes in gait, speech, or arm movement, suggesting motor involvement, are also infrequently seen. Changes in ECG and myocardial infarct have been reported, and it may be that these persistent effects are results of prolonged hypoxia, rather than direct effects of the H_2S on neural or cardiac tissue.

Lethal hydrogen sulfide poisoning exerts its effects directly on the nervous system. If the concentration of the gas is sufficiently high, the respiratory center of the brain ceases functioning and breathing stops. At the lower concentrations (between 500 and 1000 ppm), the autonomic controls of respiration whose sensors are in the carotid body are stimulated, and hyperpnea, followed by apnea, results from the instigation of the normal autonomic reflex. Asphyxiation from hydrogen sulfide results on the cellular level as the gas inhibits cytochrome oxidase and prevents the utilization of oxygen by cells, in a manner similar to the action of hydrogen cyanide. Only the uncombined, unoxidized form of the gas in the bloodstream exerts these effects. Hydrogen sulfide is not considered a cumulative poison because it is rapidly oxidized to harmless sulfates, which can be readily eliminated from the body. Hence its respiratory/asphyxiation role occurs only at higher concentrations, where, however, the effect is rapid and often fatal.

Instances of permanent neurological damage resulting from acute poisoning have been described (Aufdermaur and Tönz, 1970; Matsuo et al., 1979; Arnold et al., 1985). Included among the signs are prolonged coma, convulsions, increased tonus with extensor spasms, and Babinski's sign (Matsuo et al., 1979). Fatigue, somnolence, headache, irritability, insomnia, anxiety, poor memory, and loss of libido were reported in recovered victims (Ahlborg, 1951; Poda, 1966; Arnold et al., 1985; Illinois Institute for Environmental Quality, 1974). Also described are changes in gait, nystagmus, vertigo, and other indications of toxicity to the eighth cranial nerve (vestibulocochlear nerve) and its associated central nervous system (CNS) structures (Ahlborg, 1951). Computerized axial tomography (CAT scan) performed on a victim of acute poisoning (Matsuo et al., 1979) and post-mortem examination of brain tissue of victims suggest lesions which are characteristic of cerebral anoxia rather than any specific neurotoxicity by hydrogen sulfide (Lund and Wieland, 1966).

Changes in heart rhythms and electrocardiograms after acute hydrogen sulfide poisoning have been reported by several physicians (Drews, 1940; Krekel, 1964; Arnold et al., 1985). While cardiac muscle, like nervous tissue, has a high oxygen demand, and is highly sensitive to anoxic damage, there is a suggestion by Kosmider et al. (1967) that specific enzyme damage may result from H_2S poisoning. The accumulation of sulfate, possibly resulting from the binding of sulfide to heavy metal such as iron or to protein, has been demonstrated histochemically in brain, kidney and liver, but not heart, of guinea pigs and rats exposed to H_2S for several hours (Voigt and Müller, 1955). (See Section 8.1.4, Toxic Effects on Various Animal Tissues).

Workers exposed to H_2S concentrations between 500 to 1000 ppm exhibit a period of extremely rapid breathing or hyperpnea. From a practical standpoint, this can increase inhaled dose of gas, with resulting increased damage.

Experience with hydrogen sulfide poisoning in the fossil fuel fields of Alberta, Canada has been reviewed for the years 1969-1973 by Burnett et al. (1977) and for 1979-1983 by Arnold et al. (1985). These were retrospective studies based on the files of the Compensation Board and the files of the Medical Services Branch, Worker's Health and Safety, Calgary, Alberta, Canada; therefore only those complaints for which medical attention was sought were considered. The records contained no neurological follow-ups. Burnett et al. (1977) examined 173 cases, among which 6 percent fatalities occurred. In the 250 cases considered by Arnold et al. (1985), the fatality rate was 2.8 percent, or 7 cases. The picture of immediate toxicity from acute exposure that emerges from all of these reports is immediate respiratory paralysis and collapse at very high exposures (>2000 ppm), and collapse and apnea preceded by a period of hyperpnea at sublethal exposure (500 to 1000 ppm). The sequelae of poisoning in victims who are resuscitated vary, probably as a result of initial effect, time and intensity of exposure, and length of anoxia to vital tissues.

Recovery from acute intoxication is usually rapid and complete. Symptoms varying in nature and severity develop soon after acute poisonings and persist for different lengths of time. Poda (1966), in reviewing a number of cases described a syndrome including nervousness, nausea, headache, insomnia, and a dry, nonproductive cough which lasted for one to three days. Burnett et al. (1977) list the frequency of complaints of 173 poisoning victims in Alberta who sought medical attention (Table 8-2).

TABLE 8-2. PRESENTING CLINICAL FEATURES AFTER H_2S EXPOSURE

Feature	Observed frequency (%)		
	At accident site	At physician's office	At emergency room
Loss of consciousness	74	--	16
Disequilibrium	17	--	29
Nausea/vomiting	13	28	22
Headache	9	25	16
Sore throat/cough	8	9	14
Conjunctivitis	5	9	11
Weakness of extremities	4	--	4
Dyspnea	3	13	--
Convulsion	3	--	6
Pulmonary edema	--	--	20
Cyanosis	1	--	11
Hemoptysis	1	--	--

Source: Burnett et al. (1976). (--: not reported)

In an extension of the work of Burnett et al., Arnold et al. (1985) listed the frequency of complaints of 250 medical claims in Alberta (Table 8-3).

TABLE 8-3. CLINICAL FINDINGS RECORDED

Signs or Symptoms	Frequency of Notation	Percentage
Unconsciousness	135	54.0
Headache	65	26.0
Nausea/vomiting	62	24.8
Dyspnea	57	22.8
Disequilibrium	54	21.6
Conjunctivitis	46	18.4
Sore throat/cough	41	16.4
Felt ill	31	12.4
Neuropsychological	20	8.0
Extremity weakness	19	7.6
Chest pain	18	7.2
Pulmonary edema	14	5.6
Bradycardia	10	4.0
Convulsion	5	2.0
Cyanosis	3	1.2
Hemoptysis	1	0.4

Source: Arnold et al. (1985).

The poisoning cases reviewed by Ahlborg (1951) differ somewhat from some of these descriptions, in that sequelae of acute intoxication appeared shortly after initial acute exposure and persisted for approximately one and one-half months. In one case symptoms were still evident after three years. These patients showed symptoms such as drowsiness, fatigue, headache, lack of initiative, irritability, anxiety, poor memory, and decreased libido. They also displayed symptoms of eighth cranial nerve (vestibulocochlear) damage, such as vertigo, nystagmus, and disturbances of equilibrium.

Some of Ahlborg's cases had suffered previous episodes of exposure. Other reports in which such sequelae as well as damage to other vital tissues such as the heart were recorded (Kapainen, 1954; Hurwitz and Taylor, 1954; Kemper, 1966), involved lengthy periods of anoxia due to paralyzed respiration. Since hydrogen sulfide is rapidly metabolized and does not persist in the body of recovering victims, it is generally thought that persistent neurologic or cardiac effects are the result of anoxia to these tissues rather than a specific effect of sulfide damage.

It has been suggested by several authors that nitrites and/or thiosulfate be used in treatment of hydrogen sulfide poisoning in humans. Since hydrogen sulfide binds to the ferric ion component of cytochrome c oxidase, oxidation of hemoglobin to methemoglobin provides a ferric ion pool which competes for the hydrogen sulfide, freeing the cytochrome oxidase. Such treatment has been used successfully in cyanide poisoning, whose action with this enzyme is similar. Animal experiments by Gunter (1953), Smith and Gosselin (1966), and Smith et al. (1977) have indicated that nitrites and thiosulfate have both a prophylactic and a therapeutic effect on hydrogen sulfide poisoning. (See Section 8.1, Animal Effects). However, only a single case of human H_2S poisoning treated with these agents is published in the literature. Stine et al. (1976) report a single severe human case of hydrogen sulfide poisoning in which nitrites were used in treatment. This was of a 47-year-old man overcome by H_2S exposure with loss of consciousness and resultant seizure-like activity. He became agitated and disoriented upon recovering consciousness 30 minutes later. He was intensely cyanotic and had hyperpnea (36 breaths/min), with elevated pulse. Electrocardiographic examination showed supraventricular tachycardia and left bundle branch block. He was treated with 40 percent oxygen. Subsequent blood gas analysis showed a PaO_2 of 151 and a pCO_2 of 33 mm Hg. An anion gap of 41.2 meq/liter and a blood pH of 6.97 (severe acidosis)

was noted. The patient was treated with amyl nitrite inhalations, 30 seconds of each minute for 5 minutes; another 300 mg sodium nitrite was injected intravenously, over 3 minutes. He was also intravenously injected with 12.5 g of sodium thiosulfate. (Sodium bicarbonate was not administered). Five hours after the accident the patient was completely oriented and lucid, repeat blood gases on 40 percent oxygen showed a PaO_2 of 205 and a pCO_2 of 29 mm Hg, and a blood pH of 7.4. One month later some signs of cortical function impairment were seen, with intermittent frontal headaches, inability to concentrate, and poor attention span and poor short-term memory. After two months, neurological examination was normal, and the patient experienced only occasional headaches.

The prophylactic use of nitrites or thiosulfate on persons with potential exposure to hydrogen sulfide is not practical. Therapeutic usage, whose results are published, is limited to this single case (Stine et al., 1976). The results in this instance cannot be unequivocally attributed to the use of nitrite and/or thiosulfate, since oxygen was also used, the degree of exposure was not known, and other variables relating to recovery could have been operative.

Ravizza et al. (1982) described a case of H_2S poisoning whose clinical findings were similar to those of Stine et al. (1976). Electrocardiogram revealed a sinus tachycardia, heart rate was 140 beats/min, arterial blood gases showed hypoxemia (PaO_2 48 mm Hg), and significant metabolic acidosis existed (pH 7.21). There was the additional finding of pulmonary edema, diagnosed clinically and confirmed by chest X-ray. Intermittent positive pressure ventilation (IPPB) with positive and respiratory pressure (10 cm H_2O) and FiO_2 0.5 was administered, together with 30 mg/kg thiopental. After one hour, significant improvement in blood gases and pH occurred (PaO_2 335 mm Hg; pH 7.42). Pulmonary edema regressed. The patient continued to be unconscious but recovered full consciousness after 20 hours. The patient was discharged with no sequelae after one week.

The similarity of results seen in the comparison of these two cases lends some caution to the considerations of nitrite as the efficacious agent. The use of nitrite is not without risk, since it can induce hypotension and may add to the existing histotoxic hypoxia and the hypoxic hypoxia from pulmonary edema (Ravizza et al., 1982). Methemoglobin formation can produce hypoxemia, further compromising an already stressed individual.

8.2.2 Sublethal Concentrations

The typical "rotten egg" odor of hydrogen sulfide is detectable by the olfactory sense of humans at very low concentrations in the air (0.025 ppm, or 0.035 mg/m^3). Except as a nuisance factor with subjective responses of malaise or nausea, there is no medical evidence that H_2S significantly affects human health at this concentration. The low detection threshold may give a false sense of security that danger can be averted when the gas is smelled. At concentrations of 150 ppm and greater (>210 mg/m^3), however, the olfactory sense is paralyzed so that this supposed warning signal is effectively neutralized.

Sublethal exposure is characterized by local irritation, perceived first by the eyes then by the respiratory tract. Rochat (1923) described lesions of the cornea, seen with slit-lamp illumination, of workers in a sugar beet processing plant. Lesions as he described then were also seen by Barthelemy (1939) and Masure (1950) with exposed viscose workers, and in the gas industry by Carson (1963). Nesswetha (1969) gives an excellent description of the progression of lesions of the eye which begin after 4 to 5 hours exposure to 20 mg/m^3 (28 ppm) H_2S. Slit lamp examination first reveals a slight, grayish opacity with petechial stippling of the superficial cell layer of the cornea. The lesions are due to swelling and blistering of the epithelial cells, rather than cellular infiltration. As the injury progresses, vacuoles form in the cells, which burst and produce epithelial defects which spread and join to form larger and very painful ulcers on the corneal surface. Concomitant with the progress of the corneal keratitis there occurs an inflammation of the conjunctiva, which become injected (reddened). The lesions generally heal without permanent damage, except in very extreme exposures in which the erosion of the corneal surface can leave scars. Injury to the eyes is generally restricted to the cornea and conjunctiva. Subjective symptoms are most commonly described as a fogging or blurring of vision, the perception of colored, rainbow-like rings around lights, tearing, sensation of foreign bodies in the eye, photophobia, pain in and behind the eyes, and blepharospasm. All the above-named authors agree that ocular symptoms are the earliest seen in subacute H_2S exposure, and that they appear before any complaints of respiratory difficulties are made.

H_2S exposure can cause loss of the corneal reflex and anesthetize the surface of the eye, so that pain and irritation may not be immediately felt

upon exposure. Vision is often affected first, with changes ranging from perceived halos or rainbows around lights to "blue" and blurred vision. Damage to the conjunctiva and corneal epithelium (apparent by reversible, except with repeated insult) results in "sore eye" or "gas eye," an intensely painful manifestation of inflammation that occurs after the initial loss of sensation passes, which is accompanied by visual changes. In severe form, actual ulceration of the cornea occurs, leading to scar formation and permanent impairment of vision.

Not only are the mucous membranes of the eye affected, but sublethal concentrations of H_2S can also produce irritation of the respiratory tract resulting in bronchitis, rhinitis, pharyngitis, and laryngitis (Yant, 1930; Barthelemy, 1939; Milby, 1962; Arnold et al., 1985). Biesold et al. (1977) performed an electron microscopic examination of several regions of lung tissue excised from a 7-year-old boy who died 24 hours after being exposed to H_2S vapors from an old-fashioned farm latrine. A severe alveolar and interstitial edema of the hemorrhagic type was found. Analysis of the structural elements of the alveolar septa gave evidence of a direct toxic effect of H_2S on the endothelial and epithelial barrier of the alveoli, which permitted plasma and blood cells to infiltrate the interstitial and alveolar space. There was widespread damage to the squamous epithelium, resulting in partial denudation of the basal membrane. Indications of endothelial gaps were found, and these were often covered with microthrombi.

Milby (1962) and many other authors indicate that pulmonary edema can result from prolonged exposure to H_2S concentrations as low as 50 ppm. At exposures of 250 to 300 ppm or more, pulmonary edema almost always results, which can be life-threatening. In prolonged low-level exposure such pulmonary edema may result without accompanying systemic symptoms.

8.2.3 Toxic Effects Associated with Repeated Exposure

At concentrations between 10 and 20 ppm (14 to 28 mg/m^3), exposure over time may cause irritation of mucous membranes of the respiratory tract and the eyes. It is not entirely clear whether other chronic effects exist. Whether or not "chronic poisoning" exists as a pathologic entity or is a subjective response to an obnoxious odorant, is an unresolved issue. Also unresolved is whether those signs and symptoms that are reported result from continuous low-level exposure, or occur from damage done by isolated (and usually unmeasured)

peak high-level exposure. Further complicating the picture is that all of the occupational studies performed with low-level, chronic exposure involve exposure to other toxic gases such as sulfur dioxide, carbon disulfide, mercaptans, sulfuric acid mist, and mixtures of volatile organic compounds that individually or in aggregate elicit similar complaints. Other work conditions involved in the occupations studied, such as night work, high humidity, and temperatures, may further confound analyses.

The National Research Council (1977) defines chronic intoxication as effects from intermittent exposure to low to intermediate concentrations of H_2S in the range of 50 to 100 ppm (70 to 140 µg/l). The Illinois Institute for Environmental Quality (1974) describes chronic poisoning as a prolonged exhibition of symptoms which results either from an extended single exposure or repeated, short exposures which do not produce symptoms of acute or subacute poisoning. The symptoms include local irritation of the eyes and respiratory tract, bradycardia, cold sweats, fatigue, gastrointestinal disturbances, sleep disorders, headaches, inability to concentrate, chills, mental depression, and abnormal peripheral reflexes indicative of depression of nervous system function (Vigil, 1979).

Ahlborg (1951) studied five cases in the shale oil industry thought to involve chronic poisoning. The patients showed the symptoms previously described, but three of the five suffered from existing neurologic disease, had shown psychogenic responses during examination, and may have been responding stressfully to a potentially dangerous work environment. The authors further compared the work history and frequency of reported objective and subjective symptoms among two groups of refinery workers. One group was characterized by daily exposures, the other by rare exposures to H_2S. No significant differences in frequency of non-occupational diseases, accidents or objective signs of poisoning were observed between the two groups. However, frequency of neurasthenic symptoms such as loss of appetite, poor memory, dizziness, irritability, itching, headache, and fatigue was greater among the group of exposed workers. The author could not determine whether these symptoms resulted from the H_2S exposure or from the stressful environment.

Similar symptoms were reported by Barthelemy (1939) and Rubin and Arieff (1945) in studies in the viscose rayon industry. These workers were exposed to mixtures in which carbon disulfide predominated, but which also contained H_2S. These researchers also could not separate the indicated symptoms from work

stress, nor could they attribute them to H_2S exposure exclusively. Glebova (1950) reported that infants who were exposed to hydrogen sulfide emanating from their mother's clothing during breast feeding showed a spectrum of signs and symptoms. The mothers worked in an artificial silk factory where they were exposed to H_2S and CS_2 (carbon disulfide). When the mothers were moved away from H_2S exposure, their infants' symptoms cleared. Concentrations of 0.028 to 0.055 mg/m^3 H_2S were measured during breast-feeding times. No attempts to measure CS_2 were made. Affected babies showed poor or retarded development, low weight gain, and listlessness. Some also showed lack of animation, anemia, paleness, regurgitation after feedings, and gastrointestinal distress. Susceptibility to infectious disease was also increased.

The methods in this Russian study were not clearly delineated, and no control population comparisons were made. The effects described were not adequately related to H_2S exposure, and effects from other toxic agents, work conditions, or other confounding factors were not ruled out. Consequently, attribution of observed effects to H_2S should be viewed with strong reservations.

Kangas et al. (1984) investigated the results of H_2S, methyl mercaptan, and dimethyl disulfide exposure in ten different cellulose mills in Finland. Concentrations ranged from 0 to 20 ppm H_2S, 0 to 15 ppm methyl mercaptan, and dimethyl disulfide up to 1.5 ppm. SO_2 concentrations reached 20 ppm in some locations. Exposed workers reported headaches and decreased ability to concentrate more often than matched controls. Sick leaves also occurred more frequently among the exposed groups than in controls.

Ferris et al. (1979), Chan-Yeung et al. (1980), and Higashi et al. (1983) examined respiratory effects in workers in a pulp and paper mill in the U.S., one in Canada, and in 18 viscose rayon plants in Japan, respectively. Ferris found no significant mortality or morbidity for respiratory symptoms or illness in his study; no increases in respiratory symptoms were found by Chan-Yeung et al., nor did Higashi et al. detect increases in respiratory symptoms or decreases in pulmonary function in their study populations. It should be noted that the workers in these studies were exposed to a mixture of potentially hazardous compounds. The levels of hydrogen sulfide measured in these exposures were very low: <4 ppm in Ferris et al. (1979); <0.2 ppm, with mean of 0.05 ppm in Chan-Yeung et al. (1980); and an average of 3 ppm (0.3 to 7.8 ppm, range) in Higashi et al. (1983).

Tenhunen et al. (1983) investigated the effect of worker exposure to hydrogen sulfide and methyl mercaptan on heme synthesis. (Heme forms part of the hemoglobin complex.) Venous blood collected from 17 workers in pulp production where H_2S concentrations ranged from 0.05 to 5.2 ppm (8 hour time-weighted average), with methylmercaptan ranging from 0.7 to $\geq$1.0 ppm TWA and dimethyl sulfide in ranges from 0.03 to 3.2 ppm. Enzymes in the heme synthesis pathway (α-amino-levulinic acid synthetase and heme synthetase) showed decreased activities in eight and six cases, respectively. Erythrocyte protoporphyrin (a precursor of heme) was decreased in seven cases. None of the workers had clinical anemia. The authors attributed these changes to hydrogen sulfide exposure, but were not able to establish whether repeated peak or continuous low-level exposure occurred. No unusual complaints were recorded for any workers in the test or control groups.

Probably the most widespread and common complaint of persons exposed to low concentrations of hydrogen sulfide for short or extended periods of time are those related to odor. An extensive discussion on the psychological and aesthetic aspects of odor in general, and specifically applying to the odor of hydrogen sulfide, is included in the National Research Council (1977) monograph on hydrogen sulfide. Hydrogen sulfide has a lower limit for detection of odor of 0.003 to 0.02 ppm. At concentrations up to 30 ppm, hydrogen sulfide has an odor like that of rotten eggs, while at 30 ppm the odor is sweet or sickeningly sweet. At 100 ppm and above, hydrogen sulfide quickly fatigues the sense of smell and at concentrations approaching 150 ppm abolishes odor sensation, apparently by anesthetizing the olfactory nerve (Indiana Air Pollution Control Board, 1964). People who have survived exposure to sudden, high concentrations reported either no awareness of odor at all, or a sickening sweet smell before their loss of consciousness. The assumption that odor will warn of levels of hydrogen sulfide that are life-threatening is unwarranted, since instantaneously introduced doses (>150) are not perceived at all (Ahlborg, 1951).

Dysfunction of the vestibular portion of the vestibulocochlear nerve and its associated CNS connections has also been reported in some cases of exposure. This manifests itself as dizziness, loss of equilibrium, nystagmus, and disturbances of gait or movement and occurs at exposure at 2500 ppm (700 mg/m^3) H_2S. (Poda, 1966; Arnold et al., 1985). Exposure to H_2S has been associated with falls causing secondary injury, even death, which may be attributed in part to this neurologic effect (Arnold et al., 1985).

Another nervous system effect is hyperpnea, or very rapid breathing, which occurs usually at exposure to concentrations of 500 to 1000 ppm (700 to 1400 mg/m^3), and results from an initial effect of absorbed H_2S on the carotid bodies (Ammann, in press). Stimulatory impulses from these autonomic sensors to the respiratory center induce rapid breathing (Ammann, in press). Effect of H_2S on the respiratory centers directly causes apnea, or cessation of breathing.

8.2.4 Summary of Human Health Effects

At sufficiently high concentrations ($\geq$1000 ppm), hydrogen sulfide is rapidly fatal to humans, causing respiratory paralysis and apparent inhibition of cellular respiration. At levels between 500 and 1000 ppm, a period of rapid breathing (hyperpnea) is followed by cessation of breathing (apnea) and death. Damage to organs and to the nervous system can result from the anoxia caused by depression of cellular metabolism at levels above 250 ppm. At lower concentrations (50 to 100 ppm), the immediate and prolonged effects are irritation with inflammation of mucous membranes, particularly of the eye and the respiratory tract. Pneumonitis can result in pulmonary edema, which can be a threat to life. Though ambient concentrations tend to be below those considered harmful to human health, no long-term, low-level epidemiological studies have been done to determine whether hydrogen sulfide causes pulmonary changes similar to those caused by other irritant gases such as oxides of nitrogen and sulfur. At very low concentrations, offensiveness of odor, with mostly subjective reactions to stench, is the dominant effect (See Table 8-4).

While considerable interest in human health effects was evident during the 1920's, very little new information has been added since then. Essentially, no human health data and practically no experimental data on long-term exposures at low levels exist. No epidemiologic studies relating to cancer, teratogenesis, or reproductive effects have been done.

TABLE 8-4. EFFECTS OF EXPOSURE IN HUMANS AT VARIOUS CONCENTRATIONS IN AIR

Clinical Effects	Level of Hydrogen Sulfide ppm	Level of Hydrogen Sulfide mg/m^3	References
Odor Perception Threshold	0.003 - 0.02	0.004 - 0.028	Indiana Air Pollution Control Board (1964)
Offensive Odor of Rotten Eggs	<30	<42	Ahlborg (1951)
Offensive Odor (Sickening sweet)	>30	>42	
Occupational Exposure Limit (O.E.L.)	10	14	National Research Council (1977)
Serious Eye Injury	50 - 100	70 - 140	National Research Council (1977)
Olfactory Paralysis	150 - 200	210 - 350	National Research Council (1977)
Pulmonary Edema, Threat to Life	300 - 500	420 - 700	National Research Council (1977)
Strong Nervous Stimulation of Respiration	500 - 1000	700 - 1400	National Research Council (1977)
Respiratory Paralysis, Immediate Collapse, Death	1000 - 2000	1400 - 2800	National Research Council (1977)

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9. CARCINOGENICITY

No long-term chronic studies for carcinogenic effects have been done with H_2S. Weisburger et al. (1981) conducted a long-term bioassay of the toxicity and cancer-causing potential of a number of industrial chemicals, including sodium sulfide (described as sodium bisulfide: $Na_2S \cdot 9H_2O$). Sodium sulfide was administered by gavage to Charles River-CD rats at doses of 9 or 18 mg/kg, in the presence and absence of a 1 percent thyroid extract (to guard against possible thyroid gland impairment by sulfide). Doses were administered twice a week for 56 weeks and 2 to 3 times a week for the remaining 22. After the 78 weeks of treatment, the animals were observed for 26 weeks and then sacrificed. There were 26 male and 26 female rats per treatment group. No statistically significant evidence of carcinogenicity was found in the treatment groups, although the low survivability in groups treated with thyroid extract made the results ambiguous. The dose ranges tested, which caused some lethality in males but not females, are not completely acceptable, but they did approach the minimum toxic dose required for chronic bioassays in rats. Because of the lack of adequate animal test data, this compound is placed in category D, based on the weight-of-evidence criteria in EPA's Carcinogen Risk Assessment Guidelines issued in August, 1986. A category D ranking means that the available data is inadequate to assess a chemical's carcinogenic potential.

9.1 REFERENCES

Weisburger, E. K.; Ulland, B. M.; Nam, J.; Gart, J. J.; Weisburger, J. H. (1981) Carcinogenicity tests of certain environmental and industrial chemicals. JNCI J. Natl. Cancer Inst. 67: 75-88.

10. MUTAGENICITY

A study by Gocke et al. (1981) suggests that H_2S may have mutagenic potential. Using the Ames test with Salmonella typhimurium TA 1535, these researchers found evidence of weak mutagenicity as shown by the number of revertants to wild type for this mutant strain of bacteria, which grows only in the absence of histidine. Addition of the S-9 microsomal fraction from the liver of Aroclor-pretreated rats abolished the effect. Since only a single tester strain was used and cytotoxic records were not provided, and since there may have been confounding effects introduced by different growth media, it cannot be unequivocally stated that evidence of mutagenicity by H_2S exists.

10.1 REFERENCES

Gocke, E.; King, M.-T.; Eckhardt, K.; Wild, D. (1981) Mutagenicity of cosmetics ingredients licensed by the European Communities. Mutat. Res. 90: 91-109.

11. REPRODUCTIVE EFFECTS AND TERATOGENICITY

The teratogenic potential of hydrogen sulfide has not been studied. One report (Barilyak, 1975) describes weak embryo toxicity and teratogenic effects in rats ("unpedigreed") as a result of exposure to a 10-mg/m^3 mixture of H_2S and carbon disulfide. No concentration for H_2S was given and details concerning methodology were missing. There is a possibility that carbon disulfide in itself may be teratogenic (Beauchamp et al., 1983), so that these results are confounded (Beauchamp et al., 1984). No reproductive studies have been identified in the literature.

11.1 REFERENCES

Barilyak, I. R.; Vasilieva, I. A.; Kalinovskaya, L. P. (1975) Deistvie malykh kontsentratsii serougleroda i serovodoroda na vnutriutrobnoe razvitne u krys [Effects of small concentrations of carbon bisulphide and hydrogen sulphide on intrauterine development in rats]. Arkh. Anat. Gistol. Embriol. 68: 77-81.

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